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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 30 1955

ORDER AND DISORDER IN PULMONARY FUNCTION*

BY

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One of the most striking developments of the last fifteen years has been the steady invasion of the clinical practice of pulmonary disorders by physiological thought. Previously, and indeed to some extent currently, the effects of lung disease were discussed in terms of alteration in structure as revealed by the morbid anatomical specimen and the radiograph, features which, important as they are, provide a quite inadequate basis for comprehending the mechanism of the disturbances of disease. In this respect the respiratory system has lagged considerably behind the disorders of the heart and greater circulation, the kidneys, and the liver. Many reasons could be advanced in explanation of this conspicuous gap in clinical physiology, such as the relative reluctance of pure physiologists to use man in health and disease as a basis for fundamental research, and the relative reluctance of clinicians to bring to their practice the principles, philosophy, and quantitative weapons of pure physiology. There have, of course, been notable exceptions in both categories.

During the last ten to twenty years, however, the position has changed out of all recognition; more and more clinical scientists and physiologists are turning to the problems of respiratory function in man, and many clinicians are using physiological methods both of thought and of observation in lung disease. The stimuli for this have come in several ways: firstly, as the result of the striking success this approach has made in other fields of medicine; secondly, as the result of the demands made by the environmental extremes of high flying and deep diving; thirdly, the growing scope of pulmonary and cardiac surgery rendered possible by antibiotics, improvements in anaesthesia, including hypothermia, and widening surgical technology; and, fourthly, the ability to measure in man the variables the integration of which constitutes the patterns of adaptation in pulmonary function.

We must all at one time or another have come under the influence of Joseph Barcroft either personally—alas, not to any extent in my own case—or indirectly through his papers, and particularly through his book entitled *Features in the Architecture of Physiological Function* (1934) in which he outlined most vividly such basic principles of the mechanism of functional equilibrium or homoeostasis as the "all or none law," and the fact that adaptation is usually an integration of several adjustments which when added together cushion the internal environment against surprising ambient extremes or severe internal disabilities. I believe there are now enough data available on pulmonary function in health and disease to make it a profitable exercise to apply these principles to certain selected situations encountered in lung disorder. In attempting this I am acutely conscious of my own shortcomings, as my active interest in this field dates only from the end of the war; furthermore, my own contributions have been negligible. However, I have had the good fortune to have gifted and energetic colleagues, such as Donald, Wade, Bishop, d'Abreu, Whitfield, and Armitage, in whose work I have played little part other than that of an appreciative onlooker. Any virtues my discourse may have are theirs, while its inadequacies are my own.

Before considering the effects of disease it is necessary to outline modern belief in pulmonary function, with particular emphasis on quantitative aspects. Concerned as it is with such relatively simple processes as ventilation, gaseous diffusion, and capillary flow, the lung can be represented as a physico-mathematical image. Although the various formulae applicable to lung function are rigorous and precise in their implications, much uncertainty exists in the measurement of many of the factors upon which they are based; nevertheless it is possible in many situations to deduce the approximate values and their likely limits of variability so that the orders of magnitude of most of the variables can be deduced. In discussing these measurements I will attempt to indicate the relative cost of the work in terms of technical skill, time, and feasibility as a routine procedure in healthy and sick humans. The majority of respiratory studies are such as can be satisfactorily performed only by those experienced in human physiology or by the clinician experienced in this branch of physiology.

As a functional description it is hard to improve on that of Richard Riley (1951): "The lung is an organ into which inspired gas and mixed venous blood are pumped, in which the gas and blood are distributed to the alveoli where, by diffusion, equilibrium with respect to carbon dioxide and oxygen is approached and out of which expired gas and arterial blood pour forth."

THE ALVEOLO-CAPILLARY MEMBRANE

Let us first of all concentrate on the air–blood interface at the alveolar capillaries. The amount of oxygen which

*The first Oliver-Sharpey Lecture for 1955, delivered to the Royal College of Physicians of London on March 17.

diffuses into the blood per minute for each 1 mm. Hg pressure difference is termed the diffusion capacity, and can be expressed thus

$$D_{O_2}=\frac{\dot{V}_{O_2}}{P_{AO_2}-\bar{P}_{CO_2}}$$

where D_{O_2}=diffusing capacity, $\dot{V}_{O_2}$=amount of oxygen in millilitre diffusing per minute, and $P_{AO_2}-\bar{P}_{CO_2}$=the mean pressure gradient of oxygen in mm. Hg between the alveolar gas and the alveolar capillary blood.

In a later section consideration will be given to the question of the variability throughout the lungs of the gas gradient, but, assuming that it is equal—that is, that alveolar ventilation is uniform and the mixed venous blood is evenly distributed—then the factor D_{O_2} is a function of the area of the blood–gas interface and the thickness of the intervening membrane. This thickness comprises the total distance between the inner surface of the alveolar wall and the point in the haemoglobin molecule where oxygen enters into chemical union. Such an O_2 molecule therefore traverses the alveolar epithelium (if that be a reality and not a histological artifact), the capillary wall, a film of plasma, the envelope of the erythrocyte, and some distance into the substance of the red cell, depending on how far it has to go to find a molecule of reduced haemoglobin. So far as can be gauged from histological studies this diffusion distance is of the order of 2–4 μ, and in healthy lung is at its minimum value—that is, any pathological change, with the possible exception of those in emphysema—is likely to increase rather than diminish this distance.

The rate of diffusion of a gas through tissue is directly proportional to its solubility and inversely proportional to the square root of its molecular weight. The latter factor may be neglected, as the molecular weights of O_2, CO_2, and N_2 are 32, 44, and 28 respectively, but the solubility factor is of great practical importance. It is always assumed—and there seems little reason to dispute it—that the diffusion medium is aqueous. Indeed, it is an axiom of biology that "life is a phenomenon of matter in an aqueous medium." Now carbon dioxide is about 25 times more soluble than oxygen, and therefore it diffuses approximately that number of times more easily. Even although the diffusion gradient (taken at the beginning of the capillary) for CO_2 is from 46 mm. Hg (P_{ACO_2}) to 40 mm. Hg (P_{CCO_2})—that is, only 6 mm. as compared with approximately 60 mm. in the case of oxygen—carbon dioxide can be relied on to diffuse adequately despite any increase in distance possible within the limits of viability.

CO_2 retention in the body, as in emphysema, is not the result of impaired diffusion in respect of either rate or gradient, but is due to defective alveolar ventilation raising alveolar CO_2, resulting in its accumulation in the blood to a level sufficient to preserve the normal excretory diffusion gradient. Diffusion distance in the case of oxygen is much more likely to become a limiting factor. A practical application of these diffusion characteristics of CO_2 is that in a patient with anoxaemia but not actual respiratory failure the discovery of a high CO_2 tension in the arterial blood is proof of long-standing impaired alveolar ventilation. It is clear, therefore, that in normal people or in those in whom disease has not altered the diffusion distance the diffusion capacity is a simple function of the total active capillary area, and if by exercise the measurement becomes maximal then this maximal diffusing capacity indicates the available capillary area.

MEASUREMENT OF DIFFUSION CAPACITY

Let us turn now to the measurement of the numerator and denominator of the simple equation, the solution of which is the diffusion capacity. It is interesting to note that the history of the struggle to make these measurements satisfactorily recalls one of the great controversies of physiology—the question of whether the absorption of oxygen was at all times determined simply by diffusion or whether there existed in the gas–blood barrier of the lungs some mechanism whereby oxygen could be transferred or "secreted" from a low-tension to a high-tension zone. This was a most fruitful debate, leading to great advances in quantitative knowledge, and it may be said to have done for respiratory physiology what the "secretion versus absorption" controversy in relation to tubular function did in the much more complex field of renal physiology.

No problem arises in measuring the numerator whether it be oxygen or any other gas, but the denominator is another matter. This latter factor requires a knowledge of the gas tension in the mixed venous blood entering the capillary and of the mean capillary tension—that is, the tension which if it were present throughout the length of the capillary would result in the transfer of the same amount of gas as actually passes in diminishing quantity as the blood gas levels approximate towards the venous end of the capillary. None of the relatively insoluble inert gases such as nitrogen or helium are any use for this purpose, as they achieve air/blood equilibrium long before the blood reaches the venous end of the capillary.

Fortunately there are two gases, carbon monoxide and carbon dioxide, whose properties enable the higher and lower parameters of this alveolo–capillary diffusion gradient to be determined.

Carbon Monoxide

Carbon monoxide has proved a most versatile tool in this field because of the great affinity that haemoglobin has for it. When inhaled in low concentrations of the order of 0.5% *in air* it enters into chemical union with the haemoglobin so rapidly that it fails to attain a significant tension in the intervening plasma, with the result that the second factor in the denominator P_{CCO} becomes zero and the gradient becomes simply alveolar CO tension (P_{ACO}). If the relative molecular weights, specific solubilities, and affinities for haemoglobin are known, values obtained for carbon monoxide can be converted to those for oxygen. Although carbon monoxide was used in this field as early as the last decade of last century, notably by Haldane (1895), its application to this problem of determining the mean diffusion gradient was first reported by Bohr (1909), who used it in an attempt to determine the "secretion" controversy.

Although nothing can detract from the brilliance of the concept, it is unfortunate that he should have come to the conclusion that diffusion alone could not account for the transfer of oxygen during exercise at high altitude. This error was due to failure to recognize the increase in diffusion capacity that occurs during exercise. The same method was developed by Marie and August Krogh, and the paper by the former (Krogh, 1915) is the prototype of methods of estimating diffusion. The subject takes a large breath of air containing a small proportion of CO (less than 0.5%), quickly expires to about the mid-point of a vital capacity, holds the breath for a known time of around 6–10 seconds, and then expires completely. Samples of air collected from the ends of the first and second expirations are taken as representative of alveolar air at the beginning and end of the known period—that is, their CO contents represent the first and last diffusion gradients from which the mean gradient is calculated by the integral calculus, assuming that the velocity of diffusion is proportional to concentration. If the total volumes of gas in the lungs at these two levels are also known, the amount of CO absorbed can be calculated, and hence its diffusion gradient, and by deduction that for oxygen ascertained.

A disadvantage of this method, and I think the author realized it, was the deep breathing and breath-holding. This can have an effect on pulmonary blood flow and therefore on the amount of gas absorbed. For instance, Armitage and I (1949a), when working on the problem of air distribution in the lungs, rediscovered the fact that a single vital capacity inspiration caused the absorption of an excess volume of oxygen of the order of 30–40 ml., which could have been caused only by the drawing into the lungs of a large amount of mixed venous blood. Later applications of

the CO method by Filley *et al.* (1954) avoid the large breath manœuvre. It may be that this large breath element accounts to some extent for the fact that Krogh obtained higher values for the resting diffusion capacity than later workers, while the values for exercising diffusion capacity, when the lung blood flow is larger, are in closer agreement. That this factor is important is doubted by Forster *et al.* (1954), who provide a very able critical analysis of the factors governing CO uptake from the lungs.

The fundamental researches of Roughton (1945) have added precision to this use of CO by recognizing and circumventing the fact that in many circumstances there is an appreciable back pressure of CO at the venous end of the pulmonary capillary. Indeed, the culmination of a long series of investigations by Roughton (1945) was a brilliant exploitation of the fact that the uptake of CO by haemoglobin was substantially retarded by breathing it in a mixture with oxygen instead of air. The velocities of the reaction $Hb \rightleftharpoons CO$ were used to construct simultaneous equations from which were derived the mean time blood spends in passing through the exchange portion of a lung capillary. The figure was 0.75 (range ± 0.25) second for normal men at rest, and 0.34 (range ± 0.1) second during hard work; this important measurement constitutes an essential parameter in any quantitative concept of pulmonary function.

Carbon Dioxide

CO_2, the second gas of key importance in diffusion gradient measurements, is, as we have already noted, so diffusible that blood leaves a lung capillary so close to equilibrium that hardly any appreciable gradient remains. Therefore the comparatively easily measurable CO_2 tension of arterial blood can be taken as indicating its alveolar tension. This circumstance is the essence of the method of calculating the diffusion constant devised by Lilienthal *et al.* (1946), in which air is breathed normally until a steady state is achieved first at room air concentration and then at a low concentration. An indwelling needle enables arterial blood to be sampled. Inspired air has a known O_2 tension, while from samples of expired air O_2 consumption and the exchange ratio, or R.Q., can be estimated. The CO_2 and O_2 tensions of the arterial blood samples are measured by the bubble technique of Riley *et al.* (1946). The alveolar CO_2 is taken as the same as that in the arterial blood, and this value, along with that of the R.Q., enables the "ideal" alveolar O_2 tension to be calculated. The O_2 tension in the venous blood drawn from the pulmonary artery can be similarly measured from a sample withdrawn through a catheter, although in the original work on this technique catheterization was not employed and a value for the O_2 tension of mixed venous blood was assumed. No great error can result from this, as the slope of the dissociation curve of oxyhaemoglobin at this level of saturation indicates a restricted tension range over a wide range of saturation values.

Data are now complete for the estimation by a graphic integration method of the mean alveolo-capillary gradient—that is, the O_2 tension is known both at the entrance and the exit of the capillary, and the tension to which it is exposed throughout its transit is also known. By making these observations during a steady state, breathing both room air and air with a low O_2 content (75 mm. O_2), deductions can be made from the data which indicate how much of the pressure gradient across the alveolar membrane is due to the diffusion characteristics of the membrane and how much is simulated by the discharge into arterial blood of venous blood from bronchial veins, arteriovenous pulmonary shunts, Thebesian veins, and passage through poorly ventilated (dead-space) alveoli, etc.

Estimation of the Diffusion Constant

It is quite clear that the measurements necessary to determine the pulmonary diffusion constant require good teamwork from the operators and some collaboration from the patient. It is essentially the sort of procedure for performance in the clinical research laboratory by a team of collaborators on selected patients whose intelligence and insight are adequate. It is not and never can be the sort of test like the blood urea, which by completion of a slip can be obtained from the hospital biochemist.

Now, what inferences may be drawn from the estimation of the diffusion constant at rest and during exercise in health and disease? Krogh (1915) got values of 23 to 43 at rest and 37 to 56 during exercise, while Lilienthal *et al.* (1946) estimated it to be 12 to 36 at rest and 50 to 76 while exercising. Various studies have been made of the correlation between the diffusion capacity and the level of O_2 consumption. Riley *et al.* (1954) found in two younger people that the diffusing capacity rose sharply at levels of O_2 consumption between 600 and 1,200 ml./min., and thereafter no further increase occurred up to levels of 2,200 ml./min. In an older man these changes took place at lower levels of activity, the increase occurring with exercise at 500–900 ml. a minute O_2 and achieving a maximum at about 1,200 ml./min. It seems likely that the chief mechanism for the augmentation of the diffusion capacity is the opening up of new capillaries with perhaps a slight diminution of the diffusion distance by lung-stretching, and not the dilatation of capillaries already open, as that would result in the axial stream of blood suffering the disability of an increased diffusion distance. The fact that diffusion capacity increases up to a certain level of exercise may be the obverse of the coin, the other side of which depicts pulmonary blood flow during exercises increasing up to a certain level without substantial rise of pressure. Each may indicate the upward limit of the distensibility of the pulmonary vascular bed.

Cohn *et al.* (1954) have studied the maximal diffusing capacity in 21 normal subjects ranging in age from 17 to 76 years. The striking feature which emerged from the study was the decrease in diffusing capacity with age. Although there was a considerable scatter in the results, they were able to calculate a regression equation which indicated a reduction by 10 units of the maximal diffusing capacity for each 18 years of age. These workers considered that this decline in the range of adaptation with advancing age was just another example of the loss of adaptability consequent upon the sclerosing processes of senescence. The increasing scatter of the data with increasing age is an expression of diminishing correlation of tissue deterioration with duration of life as age advances.

The "Non-uniformity Principle"

Before discussing the application to disease states of a knowledge of gas transfer across the alveolo-capillary barrier it is necessary to develop the concept of the "non-uniformity principle." Up till now we have visualized an ideal alveolus the behaviour of which could be regarded as representative of both lungs in that all the other alveoli were identical in structure and function. It will be emphasized later that, while the requirements of respiratory function in terms of O_2 absorbed and CO_2 excreted are precisely set by the metabolic activity of the body, there exists scope for quite wide fluctuations of respiratory exchange ratio as regards short intervals of time and space, in that some alveoli may be well perfused and poorly ventilated, while in others the reverse state prevails. What this means is that philosophically there is a fourth parameter—distribution—which must be added to ventilation, diffusion, and circulation, constituting the major physiological influences affecting the partial pressures of O_2 and CO_2 in gas and blood. Although in health there is probably a remarkable uniformity of function—that is, little variation in the ventilation/perfusion ratio or R.Q. throughout the lungs—many disease states destroy this equilibrium.

Distribution is a factor applicable to both blood and gas. A relative deficiency of blood perfusion as opposed to gas ventilation raises the amount of CO_2 excreted relative to the oxygen absorbed, resulting in an exchange ratio above that determined by the currently prevailing metabolic state. The

theoretical extreme of this distortion is a ventilated but avascular alveolus which is merely an addition to the anatomical respiratory dead space; indeed, distribution defects of this sort are expressed in terms of increased dead space. The reverse state of affairs, where an alveolus is well perfused but has impaired ventilation, greatly reduces the CO_2 excretion because of the reduction of the mean pressure gradient between blood and air; similarly, this defect, if pushed to the extreme of no ventilation, constitutes an arteriovenous shunt and is referred to as an increased venous admixture effect.

The methods, already outlined in principle, of estimating the mean gaseous gradient across the gas–blood barrier and the pulmonary diffusion constant, have been extended to evaluate on the one hand a pure diffusion defect and on the other a defect due to shunting of blood through non-respiratory channels or poorly ventilated alveoli. Fortunately, in pulmonary disorder a useful approximation to the same end of gauging the magnitude and nature of ventilation perfusion imbalance or distribution defect is achieved by measuring the O_2 and CO_2 tension of a sample of arterial blood. This can be done best by the bubble technique already mentioned, but more simply but less accurately by estimating O_2 and CO_2 contents in a Van Slyke manometric apparatus. The O_2 content can be converted to tension values from the O_2 dissociation curve of haemoglobin, while the CO_2 content, if combined with the *p*H of the blood in the Henderson–Hasselbalch equation, will yield tension. In practice the CO_2 content alone gives quite a good indication of ventilatory deficiency, as values over 60 vols.% make it probable and over 70 vols.% certain.

Pathological Reactions

Turn now to the pathological processes concerned mainly with increase in alveolo-capillary gradient and reduction in the pulmonary diffusion constant either in inverse proportion or to a greater degree as the result of reduction in the area of the blood–gas interface. The earliest efforts in the field were by Krogh (1915), who, using the carbon monoxide method already outlined, measured the diffusion constant in a variety of pulmonary diseases. The general conclusion was that this factor tended to be reduced in lung disease; however, these results can be considered as only semi-quantitative, because alveolar gas tensions were estimated on samples got by direct methods liable to serious distortion in disease states, unlike the indirect methods of Riley and Cournand (1951) and Riley *et al.* (1951). The first fruit in the field of disease of the modern methods was a report by Donald *et al.* (1952) describing the results of such studies in a group of respiratory cases, comprising mainly "pulmonary fibrosis" and emphysema. About the same time a study by Austrian *et al.* (1951) reported a more detailed clinical and physiological study of cases of "pulmonary fibrosis."

Pulmonary Fibrosis

The use of this curious rather old-world label, "pulmonary fibrosis," provides an interesting study in taxonomic evolution. Originally it was a morbid anatomical term loosely applied to any and every sclerosing process in the lungs, whether part of chronic tuberculosis, silicosis, chronic congestive failure, or merely hardening of obscure aetiology. Its very vagueness caused it to fall into disfavour, but it has now been revived by the pulmonary physiologist and given, perhaps rather arbitrarily, new and quite rigorous functional criteria.

The basic disorder which characterizes this pulmonary fibrosis is an increased alveolar diffusion gradient for O_2 due principally to increase in diffusion distance and also a reduction of the blood–gas interface. It is apt to occur in diseases which produce throughout much of both lungs an increase of tissue either by cellular proliferation or by infiltration, the swelling by imbibition of connective-tissue elements, or the accumulation of fluid in connective-tissue layers, or adhering by surface tension to the alveolar walls. There is by implication an element of chronicity in the concept, as the term is not applied to comparatively acute syndromes of pulmonary dysfunction of the impaired diffusion type, such as occurs in pulmonary oedema either of inflammatory origin due to irritant gas inhalation or of severe diffuse bacterial pneumonia, or of the congestive type due to pulmonary capillary hypertension such as is found in left ventricular insufficiency or mitral disease.

The aetiological basis of the fibrosis syndrome includes a variety of quite unrelated processes. Silicosis is occasionally responsible; radiation fibrosis as a complication of heavy *x*-radiation in the treatment of malignant tumours and the reticuloses; pulmonary sarcoidosis; occasionally as the result of diffuse pulmonary carcinomatosis; the granulomatous changes that follow inhalation of beryllium; as part and parcel of the low-grade inflammatory reaction of connective tissue (collagen) which presents prominently as scleroderma; and last, and numerically by no means least, those mysterious forms of pulmonary fibrosis which may start as a pneumonic illness of the bronchopneumonic type. It is this last-named type which is termed acute diffuse interstitial fibrosis (Hamman and Rich, 1944) and which at necropsy reveals tough, rubbery lungs with a histological picture in which the alveoli look more like gland acini, lined as they are by cuboidal cells and separated from each other by vascular connective tissue.

The definitive functional change is an increase of the alveolar O_2 diffusion gradient from its normal of 8–12 mm. Hg to as high as 50 mm. Hg breathing room-air.

It is only in severe cases that arterial blood is unsaturated at rest, but in all except the mildest it becomes unsaturated on exercise. There is little or no CO_2 retention. The other changes are either in the nature of adaptation or due to the pathological changes involving tissues other than the alveolar capillary membrane. The increased tissue thickness of the pulmonary septa greatly alters its mechanical characteristics. It presents a quite abnormal resistance to distension, so that the total lung capacity, vital capacity, and particularly the inspiratory reserve capacity are all much reduced. I once saw a striking demonstration of this while watching bronchoscopy on such a case of diffuse interstitial pulmonary fibrosis. General anaesthesia had been induced with a barbiturate and a muscle relaxant given. A tracheal tube was in position. Normally in such circumstances the anaesthetist can ventilate the lungs by gently squeezing a rubber bag attached to the closed circuit, the amount of pressure required being trifling, so little opposition to moderate distension do normal lungs present. In this case the anaesthetist was at first quite bewildered, as he had to use considerable force to effect even a moderate tidal volume. The appearance and consistency of the lungs seen at necropsy some months later amply explained this indistensibility.

Mainly because the airways remain unimpeded, the maximum ventilatory capacity is but little if at all reduced, the contour of the spirogram is normal, and prolongation of expiration and dry sounds are not heard. One important abnormality which is of great help in the clinical recognition of this syndrome is the constant hyperventilation both at rest and at such higher levels of effort as they can attain. Owing to the restricted inspiratory reserve this hyperventilation is achieved by an increase of frequency rather than amplitude. The relentless ascent on the chart of the respiratory rate line marks the slow solidification of the lungs in the progressive forms (and most of them are unfortunately so) of this syndrome. Initially, soon, late, or occasionally not at all, pulmonary hypertension develops; this is precapillary in the sense that it does not include the pulmonary capillary or transpulmonary pressure, which is normal. This is an important point in excluding mitral stenosis, which may occasionally be confused with these cases of pulmonary fibrosis in which pulmonary hypertension presents early. The radiological appearances of the lungs are usually diffusely abnormal and in detail according to the cause of the fibrosis. Occasionally substantial dysfunction may precede radiological abnormalities.

VENTILATORY DYSFUNCTION

We come now to consider the mechanism of air mixing in the lungs, the object of which is to ensure that the rhythmic process of breathing maintains the composition of alveolar air such that the O_2 gradient slopes *to* the blood and the CO_2 gradient slopes down *from* the blood. This objective must be achieved in gas-exchange rates ranging in volume from around 150 ml. per square metre of body surface at rest to around ten times that volume during violent exercise.

During inspiration environmental air is drawn through the upper respiratory tract down to the lower end of the trachea and then through a complex ramification of tubes into the alveoli. In this transit, it is to some extent preceded by or mixed with the terminal portion of the preceding expiration which filled the respiratory tract at the beginning of inspiration. On reaching the alveoli the inspired gas mixes with the functional residual gas. During expiration the terminal inspired portion of fresh air contained in the non-respiratory part of the tract—that is, the dead space—is expelled, followed by alveolar gas. It is usually assumed that during respiration the "dead space" gas is entirely refreshed, the whole flushing-out process requiring only a few hundred millilitres—that is, less than all but the shallowest tidal volumes. There is no absolutely conclusive evidence of this; indeed, some results of ours (Armitage and Arnott, 1949b) were capable of interpretation on the assumption that 500-600 ml. at least was required to effect this. Admittedly the fact that the nose was clipped in these experiments introduced an artificial element.

It is necessary at this point to define the sense in which the term "uniform" could be applied to intrapulmonary distribution of inspired gas. Comroe and Fowler (1951) have defined it as meaning that during inspiration each alveolus receives simultaneously gas of the same chemical composition and of the same volume (in relation to its pre-inspiratory volume) and that this gas mixes almost immediately with the functional residual gas in the alveolus. "Uniform" has therefore a rather narrow ventilatory implication and has evolved from studies based on the inspiration of relatively insoluble reference gases, either foreign to respiration such as hydrogen and helium, or a normal gas such as O_2 in an entirely foreign concentration as in a breath of pure O_2. If the term uniform is applied to the complete functional activity of an alveolus or of any convenient grouping of alveoli such as a lobe, then the amount and composition of blood coming into gaseous contact with the alveolar air becomes equally important. In brief, uniformity of ventilation–perfusion ratio is a wider, more exacting, and much more important expression.

Lung Air Distribution

The first question is, then, Is air distribution uniform in the sense defined? The answer is that the best available evidence indicates that it is not uniform but that, at the same time, in many normal people it approaches remarkably close to uniformity. One of the earliest contributions was that of Gréhant (1864), who studied the distribution in expired air of inspirations of a known volume of hydrogen; he found the hydrogen content of expired air to be independent of the depth of expiration, and concluded that there was uniform ventilation of the lungs. Siebeck's (1910) findings were essentially similar except that uniformity was reached only after the expulsion of approximately 400 ml. of air. Krogh and Lindhard (1917), while investigating the size of the dead space, used inspirations of pure hydrogen; they found that the last sample taken during expiration invariably contained least hydrogen, and concluded that there was a definite but slight inequality in the mixing. Sonne (1934) and Roelsen (1938, 1939), using fractional sampling of expired air after inspirations of hydrogen, also found that the concentration fell steadily to the level of the end-expiration sample.

I will relate briefly the experience of Armitage and myself (1949b) in our investigations into this problem. I do so not because they were important or substantial, but because they illustrate well enough one variety of evidence upon which knowledge of lung gas distribution rests; furthermore, we got a lot of fun from this research, and the telling of the tale may have a freshness which it is hard to instil into a review of the experience of others. We were interested in certain responses of the pulmonary circulation, and it became imperative to determine how large breaths, such as might occur in hyperpnoea, were accommodated as compared with inspiration of resting tidal volumes. There was uncertainty in our minds whether deep breaths caused a further distension of these alveoli used in quiet breathing or whether there occurred an opening of successive ranges of "reserve alveoli" which are folded up parachute-wise during quiet breathing, or even a combination of these two mechanisms. If the first hypothesis be correct and alveolar ventilation uniform, or near uniform, it should be possible to predict, after any depth of inspiration, the final alveolar concentration of an inert "reference gas" by the following formula:

$$P_3 = \frac{P_1 V_1 + P_2 V_2}{V_1 + V_2}$$

where P_1=concentration of gas in alveolar air before inspiration; P_2=concentration of gas in inspired air; P_3=concentration of gas in alveolar air after inspiration; V_1=volume of air in lungs before inspiration; and V_2=volume of inspiration.

Any systematic irregularity of alveolar ventilation would cause a discrepancy between the alveolar concentration thus predicted and that observed by analysis of an alveolar sample. Thus if the reserve alveolar hypothesis be correct, then, as the depth of inspiration increases, a rising proportion of the air inspired must enter newly opened alveoli and thus neither mix with the contents of the normally open alveoli nor contribute to the subsequent alveolar sample, on the reasonable assumption that the air expired last originates in alveoli which are always "open." This latter state of affairs would therefore show with deeper breaths a progressive deviation from the composition predicted, on the basis of the first hypothesis. The first application of this procedure was by asking a subject to respire to equilibrium in a closed circuit containing a hydrogen–nitrogen–oxygen mixture; he then took a measured inspiration of air which was expelled and an alveolar sample was collected. The observed final concentration of hydrogen did not differ significantly from the predicted concentration. A similar experiment was performed, using nitrogen as the reference gas. In this instance the subject first achieved equilibrium with an 80% oxygen–nitrogen mixture, so as to avoid anoxia when large measured inspirations of nitrogen were superimposed. Once again the observed concentrations were the same as the predicted. A third variation of the theme was the inspiration of varying amounts of hydrogen from the resting respiratory level. Again the mixing seemed to be reasonably uniform.

The Nitrogen Concentration Method

Another approach to this problem is to study the effect of a series of uniform breaths of oxygen on the nitrogen concentration of the alveolar gas. Obviously if intrapulmonary distribution of the inhaled O_2 is uniform the final concentration after reinhalation will be predictable by the formula

$$C_n = C_o r^n,$$

where C_n=final concentration of nitrogen after n breaths; C_o=original concentration, and r=the dilution ratio of a single breath (the proportion the breath bears to the functional residual volume). This exponential relationship can best be shown by plotting the logarithm of the final concentration against the number of breaths, when, if observed coincides with predicted, the result will be a straight line. Darling *et al.* (1944) concluded, on the basis of this method,

that mixing was reasonably uniform in normal people. Briscoe *et al.* (1951) came to a similar conclusion, using this principle applied to the progressive rebreathing of an air/helium mixture, in that they found some subjects in whom the results suggested some inequality and that the fact that they were unable to allow accurately for the effect of the dead space might conceal a degree of departure from the principle of uniform distribution.

During recent years the development of methods which enable the concentration of the reference gas to be measured, expiration by expiration, has greatly refined the application of this technique. These methods employ either the nitrogen-meter (Lilly, 1946; Lilly and Hervey, 1948) or a mass spectrograph. Using the latter, Robertson *et al.* (1950) found that all of 18 healthy people of varying ages breathing oxygen had successive concentrations of expired nitrogen such that their logarithmic plot did not fall along a straight line, but seemed to be fitted by at least two straight lines.

A third method of investigating this problem has been by the continuous analysis of a single expiration, also using the nitrogen meter. This represents a great advance on the relatively laborious methods of sampling successive portions of an expiration such as used by Krogh and Lindhard (1917), Aitken and Clark-Kennedy (1927), and Armitage *et al.* (1949). Whatever the method employed, there has always been found a slight but significantly lower concentration of the reference gas in the last expired portion of the exhalation. In our studies we interpreted this to be due to the contamination of the earlier samples by part of the preceding inspiration trapped in the dead space artificially difficult to wash out because of the clipped nose. Fowler (1949) has, however, interpreted this to be due to what is termed segmental ventilation, in which certain areas of the lung fill before and empty after other areas. This process results in a preferential distribution of the respiratory dead space gas to those regions which fill first on inspiration.

The outstanding physiological defect that is present in disease processes which partially occlude air passages or which, as in emphysema, are accompanied by gross reduction in lung elasticity is reduction of alveolar ventilation. The result is an abnormally low alveolar oxygen tension and high CO_2 tension, leading to arterial unsaturation and CO_2 retention—that is, anoxaemia and hypercarbaemia.

In conclusion, therefore, I would emphasize that pulmonary function and dysfunction in respect of alveolar ventilation and exchange across the alveolo-capillary membrane is explicable on the basis of simple physical laws.

[The second lecture, with a list of references, will be published in our next issue.]

The passing of the National Health Service Act, which placed hospitals in the public charge, made it at once more important and more feasible to try to assess the adequacy of hospital facilities provided in relation to a defined community. Since 1946 a few such assessments have been undertaken, five of them in Scotland. The first were the Nuffield surveys of hospital-treated sickness in Stirling (1948–9) and Ayrshire (1950); then came Fraser and McKinlay's in the Northern Region; the Eastern Regional Hospital Board surveyed the Dundee region in connexion with the projected new teaching centre (though the results have not been published); and the most recent relates to the sickness treated by the hospitals under the control of the Board of Management for the County and City of Perth General Hospitals during 1952. This report, by Dr. William Mackie, the medical superintendent of the group, gives a comprehensive picture of the services offered and the use made of them. Copies of Dr. W. Mackie's report: "The County and City of Perth General Hospitals: A Survey of Hospital-treated Sickness in 1952," may be obtained from the Nuffield Provincial Hospitals Trust, Nuffield Lodge, Regent's Park, London, N.W.1, price 2s. 6d. (post free).

PERSONIFICATION OF PARALYSED LIMBS IN HEMIPLEGICS*

BY

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The phenomenon of anosognosia for paralysis (or "nosoagnosia" as some prefer to call it) is a neurological commonplace. The clinical background is commonly made up of (1) a transient loss of consciousness; (2) hemiparesis or hemiplegia of abrupt onset (hence anosognosia is commoner with vascular and traumatic lesions of the brain than with space-occupying lesions); (3) a state of post-ictal confusion, not necessarily intense; (4) a left-sided paralysis, in the case of a right-handed subject; and (5) an associated defect of sensibility over the affected segments indicating an involvement of the parietal lobe.

Unawareness of the fact of being paralysed is generally a transient feature, though not always so. As a rule it is not a strictly isolated defect of insight, for the patient usually betrays other comparable traits. Thus he may make light of the severity of his illness and talk of resuming his work, or journey, or holiday in a day or two; he may not even realize that he is a sick man at all; he may be disorientated in several spheres; he may be incontinent without registering any distress or proffering any comment.

Should the paralysed patient happen also to be afflicted with a recent blindness, then it is often found that he ignores or neglects or even denies this symptom, as well as the paralysis. This is not invariable, however. The patient may be aware of some aspects of his total disability. For example, he may mention that he has become dysarthric or that his face is crooked. But the paralysis of the left arm and leg—manifestations which one would imagine were all-obtrusive—are not mentioned at all by the patient. When anosognosia embraces several associated bodily defects, including paralysis, it may be capable of experimental enhancement. Thus Guthrie and Grossman (1952) immobilized the intact right arms of two of their patients with anosognosia for a left hemiplegia. The result was that the artificially imposed restraint affecting the normal limbs now also shared in the phenomenon of denial, for the patients minimized their helplessness and tried by various excuses to explain away their non-performance.

Cause of Anosognosia

There has been no complete unanimity among neurologists concerning the nature or causation of anosognosia. Briefly there are three chief opinions about the matter: (1) That anosognosia is a specific "parietal" syndrome; furthermore, that it is the expression of disorder of the minor hemisphere; and that the minor (non-dominant) parietal lobe is more concerned with the integrity of corporeal awareness (body-image) than is the dominant half of the brain. (2) That the all-important factor is not so much the *site* of the lesion, or even the *side* of the lesion, as the degree of accompanying confusion and the nature of the previous personality. (3) That anosognosia for hemiplegia is merely the most striking and most easily recognizable

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instance of what is indeed a common and even characteristic feature of cerebral disease in general—namely, a failure to realize or admit the presence or extent of disability resulting therefrom. In other words, anosognosia is but one example of the ordinary "denial syndrome" of a neurological patient. These three conceptions constitute the main uncertainties which surround the topic.

Although the three hypotheses mentioned are often discussed as though they were mutually exclusive, this is not necessarily true. In other words, it may be a fact that anosognosia for hemiplegia is more often seen with lesions of the parietal lobe than with lesions elsewhere in the brain—though clinical exceptions may perhaps occur. Secondly, a certain type of personality existing before the hemiplegia may well play some part in determining the patient's subsequent attitude towards his disability. In other words, a denial of illness had perhaps been a lifelong pattern (Guthrie and Grossman, 1952). Thirdly, it may well be that anosognosia for hemiplegia cannot exist with a perfectly clear sensorium. Fourthly, anosognosia can also follow lesions of the dominant half of the brain—though less readily identifiable.

This last point needs closer examination. The notion that the integrity of corporeal awareness is bound up with the normal function of one cerebral hemiphere is, on the face of it, a challenge—faintly shocking to those who take a more holistic view of cerebral function.

This is not to deny that to-day many neurologists, neurophysiologists, and even psychologists still tend to parcellate cerebral function, and to relegate speech to one hemisphere and corporeal awareness to the other. Perhaps this school of neurologists is fighting what is more and more certainly a losing battle.

Defective Insight

In the matter of corporeal awareness, verbal description on the part of the patient is almost a *sine qua non* if we are to detect and record adequately the clinical phenomena of defective insight. It is indeed difficult to gauge just how much awareness a patient possesses of the nature, extent, and social implications of his disability if at the same time he is deprived of the means of communication by articulate utterance or by writing. With such aphasic patients it is only by a very shrewd appraisal, based upon close observation of behaviour, that one can glean something of their subjective attitude towards their incapacity. But aphasia is not always severe in cases of left parietal disease, and when the speech faculties are adequate, evidence suggesting anosognosia for a right hemiparesis may be detectable. A number of such cases can be quoted from the literature. Some neurologists believe that the two hemispheres are equipotential in respect of corporeal awareness and insight, and that anosognosia can be identified in right hemiplegics provided that special clinical methods of study are adopted. One can refer particularly to the observations and opinions of Dattner (1950) upon this subject.

The only attempt at a numerical survey of unawareness of hemiplegia has been carried out by Nathanson, Bergman, and Gordon (1952). From a series of 100 consecutive cases of hemiplegia, 28 patients showed various degrees of anosognosia. In 23 of these there was a firm and consistent denial of paralysis, with claims that the affected limbs could be moved. As to the sidedness of the paralysis, it transpired that 19 of the 28 (69%) were cases of left hemiplegia; 6 (or 21%) were cases of right hemiplegia with no loss of speech. There were 48 patients who showed no symptoms of denial (18 left hemiplegics, 17 right hemiplegics with aphasia, and 13 right hemiplegics without aphasia).

I have already suggested that anosognosia for hemiplegia is generally a temporary phenomenon. How long it endures depends partly upon the depth and duration of the postictal confusion. But it also depends to some extent upon environmental circumstances. The part played by nurses, relatives, and doctors is very important, for the hard fact of paralysis may be brought early to the attention of the patient; or, on the other hand, it may be glossed over or minimized for a considerable time, perhaps until the eventual return of strength to the affected limb.

It is possible to discern a number of different mental reactions on the part of the patient during the convalescent stage. As awareness of the disability gradually dawns upon the patient (or after the disability has repeatedly been brought to his notice by his attendants) we may witness diverse types of behaviour. Most abnormal of these are the various degrees of organic repression: the patient may not only be unaware of the paralysis, but he may, when questioned, even deny the fact that he is paralysed. Though these two attitudes are indices of the two very different psychological defects—the one being far more serious than the other—the same term "anosognosia" is applied to both. From denial of paralysis, the patient may even proceed to a denial of the actual ownership of the paralysed limbs. Thence he may go on to a confabulation, and he may proclaim that the paralysed limbs belong to someone else—real or imaginary; dead or alive (= personification anosognosia: somatoparaphrenia).

Some Phenomena

Nathanson *et al.* have mentioned an unusual phenomenon in this connexion, one which I personally have not yet observed. The patient may betray a disorder of language, but only when the affected left limb is under discussion. Ordinarily in no way aphasic, the patient may be at a loss for the right word, fail to carry out commands, become mute, or else use neologisms or gibberish, but only so long as the left side is being tested. This perhaps corresponds with what Weinstein and Kahn (1952) have called "non-aphasic language disturbances" or "non-aphasic misnaming" in cases of organic brain disease with denial of illness.

Much commoner, and far less abnormal, is a slow and progressive development of awareness of the paralysis. The patient may reluctantly admit that the arm and leg are weak, and then immediately go on to rationalize, and to try to explain away the cerebral dysfunction on the grounds of a non-significant peripheral defect (a sprain, an old fracture, rheumatism, sciatica). This pseudo-explanation may have a basis in fact, or it may not. In either case it is in reality quite inadequate to account for the loss of function. The patient prefers to accept a peripheral, extracerebral excuse. Or at any rate he talks that way, for how far he is fooling himself as well as trying to deceive his entourage is debatable.

Another common phenomenon of the convalescent patient who originally showed anosognosia is for him to accept the fact that he is paralysed; to concede it for what it is—namely, a hemiplegia of cerebral origin—but to make light of it. He is not euphoric in the ordinary way, but he treats his paralysis with insouciance and cheerful acceptance, even jokingly. This striking but less well-known mental attitude has been called anosodiaphoria (Babinski, 1914).

(I apologize for these terms. I know that they are offensive to some. But the alternative is worse. To coin a phrase of pure Hellenic descent, to define it clearly at the outset, then to apply it strictly and exclusively to the phenomenon under scrutiny is far better than to borrow a term which is already in common parlance, and then to torture and twist its meaning in a Procrustean fashion so as to suit one's immediate purpose. The result is then only too often ambiguity, non-comprehension, and finally error. This latter practice constitutes a grievous fault within the language of psychology and of philosophy. We ought to keep well in mind the dictum of Sir William Gowers, who said, ". . . I do not like new words—indeed, I dislike them—but if we have a conception for which no name exists, which we need frequently to speak of, it is not wise to shrink from an attempt to give it a name.")

Anastasopoulos (1954) has noted another curious phenomenon within the realm of corporeal awareness,

one which seems to him specifically to involve the limbs of the *right* side, whether that be the side originally paralysed or whether the hemiplegia be on the left. This consists in a mistaken idea that the strength of the right arm and leg has recently *increased*, so that they have now become more robust than before the stroke. Such an accession of power may be a restoration of function after a right-sided weakness; or it may be an over-development within the *intact* limbs (the left being paralysed). A previous transient unawareness of the paralysis, whether right- or left-sided, seems always to have been present. The patient's mood is typically one of euphoria coupled with unrestrained conduct. Anastasopoulos believes that the two cerebral hemispheres, when diseased, show two different types of disorder within the sphere of corporeal awareness. Exaggerated ideas of the power of the right arm are bound up with the greater functional role of the right arm in dextrad subjects, as a tool connecting personal with extrapersonal space. In his pathological cases, the right arm now changes so as to constitute "almost a part of the surroundings"—as he put it—"rather like an external object."

A Common Reaction

In this connexion I would like to describe a very common reaction which the parietal patient may display towards a long-standing and severe hemiplegia. It is an attitude which comes about long after an initial anosognosia. In some ways it can be regarded as a diametrically opposite attitude, an over-compensation perhaps. The patient has now come to accept the fact of paralysis as being present, but he appears almost detached about it, something of an onlooker. The paralysed arm and leg are regarded almost as something apart from the rest of the anatomy, like a foreign body. The crippled and useless limbs are referred to as though invested with a personality or identity of their own, but in a semi-facetious proprietary fashion, as one might look upon a plaything or a pet. The patient speaks of his arm and leg in a sort of baby-talk. He may refer to the paralysed limb as "she" or "it," while a female patient may speak in terms of "he" and "him." More often nicknames are applied to the affected limbs in a childish fashion. I have personal knowledge of patients who have called their limbs "George," "Toby," "silly-billy," "floppy Joe," "baby," "gammy," "the immovable one," "the curse," "lazy-bones," "the nuisance." The patient recently recorded by Gilliatt and Pratt (1952) would often refer to her paralysed arm as a "poor little withered hand," and she would often pick it up and kiss it. Maybe this phenomenon of personification is commoner than we neurologists realize; and practitioners, physiotherapists, and the confidants of hemiplegic patients can perhaps tell us more about this state of affairs. It is strange that it has not been described before this in the literature.

Personification of this kind often coexists with some degree of anosodiaphoria, or lack of concern over the existence of the hemiplegia. Probably in every instance unawareness of the hemiplegia came first, perhaps also a temporary denial of the paralysis. As in the case of anosognosia, a left hemiplegia is commoner than a right hemiplegia, though I have encountered at least one such case in a man who was a right-handed subject with mild dysphasia and a right-sided paralysis.

Perhaps one may seem to be labouring the argument, but the point is that, apart from hemiplegics, patients rarely adopt this curiously detached attitude towards their extremities when paralysed or otherwise afflicted. An exception is the case of the gouty librettist, W. S. Gilbert, who was in the habit of addressing his troublesome limbs as Labouchère and Clement Scott, after the respective editors of *Truth* and *The Theatre*. Amputees sometimes personify their phantom limbs. Perhaps the most bizarre non-neurological example, however, is Dr. P. Nathan's patient who used to speak of her colostomy as "George."

Still other disorders of corporeal awareness may be noted at times in hemiplegic patients, but they need not be discussed here. Such include the feeling of nothingness affecting one side (hemidepersonalization, hemiaschematia); and also the illusion as though the limb were moving; as well as the phenomenon of the supernumerary limb (phantom third arm).

Dislike of the Paralysed Limbs

Finally, it is necessary to mention yet another mental reaction upon the part of the patient towards his paralysis. Occasionally we find a patient displaying a veritable dislike of the paralysed limbs which evoke feelings of disgust, dismay, and even horror. The paralysed arm may be kept covered by the bedclothes or a shawl so as to conceal it. Or the patient may keep the gaze averted from the affected side—an attitude which is not so much an unwilled deviation of head and eyes away from the limbs as a deliberate act of revulsion: a phenomenon in the realm of psychopathology rather than physiology. To direct inquiry the patient may speak of the limbs as being horrid, ugly, unnatural, heavy, like a block of wood or a piece of dead meat. The patient may even talk as though the physical properties of the limb had actually changed, becoming shrunken, discoloured, wizened, or corpse-like.

R. S. Allison's (personal communication) patient would often involuntarily clutch with her paretic left hand the cot sides of the hospital bed. With her intact right hand she would repeatedly strike her paralysed limb, telling "it" to release its hold. Though not denying ownership of the arm, she regarded it as endowed with a perverse will of its own.

Some such reaction was displayed by a hemiplegic patient—under the care of Dr. Leonard Cox, of Melbourne—who, while I was examining her limbs, suddenly proclaimed, in the words of St. Paul, . . . "O wretched woman that I am! who shall deliver me from the body of this death?"

We are reminded of the linguistic taboo met with in many languages whereby the left hand is spoken of as something sinister or unlucky. Whereas the adjectival "right" is often synonymous with "right"—that is, the opposite of "wrong"—in some languages the left hand receives an appellation which also means "old," "weak," "tired," "crooked," "mutilated," "withered," or "flaccid" (Bonfante, 1946).

In such cases of morbid dislike of the paralysed extremities we are witnessing hypochondriacal ideas which border upon the delusional. Here we may perhaps trace the operation of an acquired cerebral lesion upon a susceptible premorbid personality. Such a patient has probably always been a candidate for hypochondriacal trends by reason of an innate preoccupation with bodily efficiency and physical fitness. Perhaps the patient was once a man of exceptional muscular prowess and of athletic proclivity. By easy stages this may in later life predispose to a certain faddiness or crankiness. The sudden development of a hemiplegia in such a subject will then constitute an affront to the *amour propre*, one which could scarcely occur in the case of the cracked pitcher, the weakling of indifferent physique. The novelist Christopher Morley was shrewdly correct in the statement which he put into the lips of Kitty Foyle: "When anything goes wrong with a man he sure lets you hear about it. If they've been athletes I guess they just think of bodies as something to have fun with, until the works begin to gum up. They don't realize, the way women have to, that it's a dam complicated piece of doings."

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ACQUIRED FIBRINOPENIA IN PREGNANCY

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The occurrence of a blood coagulation defect in certain obstetrical emergencies is now well recognized. A considerable volume of literature has accumulated on this subject, especially in North America. More recently interest in the matter has been aroused here. There can be little doubt that failure to recognize this condition has accounted for some fraction of the maternal mortality attributed to haemorrhage occurring in circumstances where good transfusion facilities were available. It is generally agreed that an acquired fibrinopenia is responsible for the coagulation defect in the clinical phenomenon under discussion, but opinions differ regarding the mechanism by which this depletion of circulating fibrinogen is brought about.

This condition is most commonly seen in accidental haemorrhage, but it occurs also from time to time in association with amniotic fluid embolism, when it may lead to fatal post-partum haemorrhage. We have encountered it, as have others, following the delivery of a macerated stillborn foetus retained *in utero* for a considerable time in a rhesus-immunized mother, and very recently we have seen the condition occur in a case of missed abortion (eight weeks). In this case no abnormal haemagglutinin was detected in the mother, who was Group O, Rh (D) positive. It is interesting to speculate on the extent to which this phenomenon may be responsible for the apparently disproportionately severe haemorrhage sometimes encountered in evacuating the uterus in cases of missed abortion. Feeney (1954) has reported two cases of vulvo-vaginal haematoma in which laboratory tests indicated a deficiency of blood fibrinogen. We have recently been led to consider the possibility that lung injury associated with the inhalation of vomitus may be another exciting cause.

If one is conscious of this problem and of its importance to the obstetrician, severe depletion of blood fibrinogen can be recognized with comparative ease. In any intractable haemorrhage complicating pregnancy repeated determination of the coagulation time by the Lee and White method should be performed. This very simple procedure will detect extreme degrees of fibrinopenia. Even when the coagulation time lies within normal limits the "clot observation test" described by Weiner *et al.* (1950) may prove valuable. We have been interested in the rapid fibrinogen assay method devised by Schneider (1952), and we wish particularly to draw attention to a simple colorimetric method for the estimation of plasma fibrinogen recently described by Shea (1954). These two methods will detect degrees of fibrinogen deficiency not recognizable by the Lee and White technique. Both are well within the compass of the small clinical laboratory.

The following cases are illustrative of the occurrence of fibrinopenia in the various circumstances already referred to.

Case 1.—Coagulation Defect Associated with Concealed Accidental Haemorrhage

A 3-para aged 24. Previous obstetric history uneventful. Had antenatal care in present pregnancy from 24 weeks. Iron-deficiency anaemia detected. Responded well to treatment. Admitted at 36 weeks with history of bleeding before admission (about 250 ml.). General condition fair, shocked, restless, B.P. 110/70. Albuminuria +2. No oedema. In fairly strong labour. Uterus enlarged to size of full-term pregnancy. Tense but not tender. Head deeply engaged; foetal heart sounds absent. Diagnosis, concealed accidental haemorrhage.

Clotting-time (Lee and White) ascertained and self-retaining catheter placed in bladder to check urinary output. Membranes ruptured. Morphine, ¼ gr. (16 mg.). Blood taken for clotting-time did not coagulate. No improvement after 3 pints (1.7 litres) of blood. Renal splanchnic block. Fifty millilitres of ½% procaine with hyalase to each renal pedicle, as only a few drops of blood-stained urine had been passed in 2½ hours despite well-maintained blood pressure. Coagulation time at 8 p.m. was 90 minutes (Lee and White). Splanchnic block was followed immediately by free secretion of urine. No further anxiety occurred in relation to renal function. Some six hours after admission following transfusion of 5 pints (2.8 litres) of whole blood the uterus was still increasing in size. Schneider, very weak—1 in 50. Two pints (1.1 litres) double-strength plasma given rapidly, intravenously, and lower-segment section carried out under local analgesia. Immediately after infusion of double-strength plasma coagulation time was reduced to 3 minutes. Schneider test showed firm fibrin clot at 1 in 50 dilution with weak coagulum at 1 in 100. An extreme degree of Couvelaire uterus was found; there were about 4 to 5 pints (2.2 to 2.8 litres) of blood in the uterine cavity. After removal of blood and extraction of foetus, uterus contracted at once and no further bleeding occurred.

Case 2

A 7-para. Non-booked. Admitted by flying squad from 60 miles. Severe combined accidental haemorrhage of six hours' duration. B.P. 150/90. Albumin +2. Foetal heart sounds absent. Transfusion (1 pint; 570 ml.) during journey in ambulance. On admission to hospital Lee and White test showed no coagulation. Transfusion continued, membranes punctured, pitocin, 3 minims (0.18 ml.). Delivery of stillborn infant 15 minutes later. Coagulation time now 4½ minutes, but Schneider titre only 1 in 10. Six hours later Schneider titre 1 in 50 (weak). After 24 hours 1 in 200 (good coagulum). Large ecchymoses appeared on both volar surfaces of forearms and on the lower abdomen during the first 72 hours of the puerperium.

Comment.—This case illustrates the sensitivity of the Schneider assay method for detecting degrees of fibrinopenia insufficient to disturb the Lee and White coagulation time. The figures quoted demonstrate the gradual replenishment of circulating fibrinogen from endogenous sources during the 24 hours following delivery.

Case 3.—Amniotic Embolism Associated with Fatal Post-Partum Haemorrhage

A 4-para. Booked case. History of previous manual removal. Admitted at term in labour. B.P. 170/90. Albumin a trace. Spontaneous delivery, living infant, 8 lb. (3.6 kg.) after 7½ hours' labour; second stage 15 minutes. Unusually strong contractions. Immediate post-partum haemorrhage with shock, slight cyanosis and short cough. Difficult manual removal of placenta, which was first-degree praevia

and was abnormally adherent over a small area. Haemorrhage continued despite usual oxytocics. Hot intrauterine douche and packing of uterus ineffective. Increasing shock. Blood transfusion (12 pints (6.8 litres) in all). In view of continuing haemorrhage and history of difficult manual removal, hysterectomy carried out. Operation very difficult, as oozing from entire field of operation could not be controlled. As the operation progressed the true nature of the condition was suspected (amniotic embolism with fibrinopenia). At this stage the laboratory staff reported that the blood samples sent for compatibility tests had failed to coagulate, and that serum for cross-matching had been secured only after centrifugation. Although pure human fibrinogen, 1.6 g., was given intravenously, haemorrhage could not be controlled, and the patient died five hours after operation.

Post-mortem Examination.—A large amount of free uncoagulated blood found in the peritoneal cavity. There was marked pulmonary oedema, but no macroscopic evidence of infarction. Histological examination confirmed the occurrence of amniotic embolus. Epithelial squames were seen in the lumina of the smaller vessels of the pulmonary circuit. No lanugo hairs were found.

Comment.—We believe that the diagnosis of pulmonary amniotic fluid embolus could have been made earlier in this case. The association of violent uterine contractions with the development of shock, cyanosis, and short cough were suggestive features. The post-partum haemorrhage following manual removal should then have been treated by blood transfusion combined with intravenous fibrinogen and the avoidance of active intervention, which served only to aggravate the bleeding. A grossly inadequate dose of fibrinogen was administered. As we have emphasized before (Barry and Geoghegan, 1954), it is quite impossible to correct gross fibrinopenia by even the most massive blood transfusions.

Case 4.—Coagulation Defect in Association with Retention of Macerated Foetus in an Rh-Immunized Mother

A 3-para aged 27. Booked case. Known case of Rh incompatibility. Husband homozygous CDe/CDe. *Previous obstetric history:* First baby, male, living. Second, induction of labour at 39 weeks; infant survived 30 minutes; severe haemolytic disease. Third spontaneous delivery at 32 weeks; hydropic infant; survived 30 minutes.

Present Pregnancy.—Admitted in labour at 37 weeks with heavy vaginal bleeding. No history of feeling foetal movement. Fundus at level of 26-weeks pregnancy. Abdomen soft. No tenderness. Clinically, missed abortion. Os dilated two fingerbreadths. Heavy bleeding accompanied vaginal examination. Small macerated foetus presenting by vertex. Bipolar version. Extraction with perforation of aftercoming head. Placenta removed by ovum forceps. Bleeding continuous and heavy during evacuation of uterus. Blood taken for Lee and White coagulation time did not clot. Transfusion begun (1 pint (570 ml.) Group O, Rh-negative) followed after 20 minutes by 1 pint (570 ml.) double-strength reconstituted plasma. Thirty minutes later Lee and White test showed weak coagulum at 8 minutes. One pint (570 ml.) blood with 10 units pitocin and 0.5 mg. ergometrine given. Blood loss diminished to slight trickle and arrested after a further pint (570 ml.) of double-strength plasma. Subsequent clinical course uneventful. The occurrence of a coagulation defect in these circumstances suggests that induction of labour should be considered immediately foetal death has occurred.

Case 5

This case is of interest because of the fact that a coagulation defect developed for no apparent reason.

A 2-para. Booked case. Admitted at term. Vertex R.O.A. Normal delivery, female living infant 6 lb. 15 oz. (3.1 kg.). Chloroform anaesthesia. There was troublesome vomiting. Normal third stage. Placenta and membranes complete. Intravenous ergometrine, 0.5 mg. Following expression of placenta there was continuous slight bleeding, though uterus was well contracted. Small perineal haematoma. Uterus and vagina explored (gas, oxygen, trichlorethylene anaesthesia). No significant trauma apparent. Uterus and vagina plugged. Bleeding continued through pack. Transfusion started. Blood taken for Lee and White clotting-time showed no coagulum at 30 minutes. Immediately a coagulation defect was diagnosed the pack was removed, being considered definitely harmful. Though uterus was well contracted a large amount of uncoagulated dark blood was expressed by pressure on the fundus. Bleeding continued. Whole blood (16 pints: 9.1 litres) given. Quadruple strength plasma (2 pints: 1.1 litres), and pure fibrinogen (1.4 g.) given. Bleeding gradually ceased. Coagulation time reduced to 4½ minutes. Schneider assay 24 hours after delivery 1 in 800 (a trace at 1 in 1,600). The puerperium was subsequently uneventful.

Comment.—There was no obvious reason why a coagulation defect should have developed in this patient. We have considered the possibility that inhalation of vomitus may have been of some significance—possible lung injury liberating thromboplastin.

Case 6.—Coagulation Defect in a Case of Missed Abortion in an Rh-positive Patient

A 1-para aged 24. Booked case. Full-term, normal delivery. Admitted for dilatation and curettage for missed abortion. Hogben test negative. Uterus had failed to enlarge beyond the size of 8-weeks pregnancy over a period of 5½ months. There was slight irregular bleeding for three weeks before admission. Routine dilatation and curettage with uterine plug at end of operation. Some three hours after operation undue haemorrhage was noted, seeping through the uterine plug. Ergometrine, 0.5 mg. (repeated), was without effect. It was assumed that evacuation had been incomplete. The patient now returned to the theatre, pack removed, and uterus re-explored. A small amount of debris removed and pack reinserted. Free haemorrhage continued. A coagulation defect suspected; Lee and White test showed no coagulation. Schneider assay showed a titre of only 1 in 10, indicating a gross fibrinopenia. Patient was Group O, Rh (D) positive. Blood transfusion of 2½ pints (1.4 litres) over a period of three hours sufficient to arrest haemorrhage, though Schneider test performed at the completion of the second transfusion was positive only to a titre of 1 in 200 (weak). Same figure obtained 15 hours later.

Comment.—Experience with this patient suggests that delay in the evacuation of missed abortion is inadvisable.

Comment on Series

The foregoing cases have been selected in order to demonstrate the various circumstances in which intractable haemorrhage due to a defect of coagulation may be encountered in obstetrics. We (Barry and Geoghegan, 1954) have emphasized that when this condition is present any form of active interference serves only to increase blood loss. The pressing indication is the correction of the coagulation defect. In minor degrees this can be achieved by energetic transfusion of whole blood. In more severe degrees, although whole-blood transfusion is essential to restore blood volume, haemorrhage cannot be arrested unless pure fibrinogen, in dosage varying from 2 to 6 g., is given intravenously. The first report of the use of pure human fibrinogen in this connexion came from Moloney *et al.* (1949). When pure fibrinogen is not available we have found that triple- or quadruple-strength reconstituted plasma is equally effective. (One bottle of quadruple-strength reconstituted plasma may be expected to yield about 4.4 g. of fibrinogen.) It may be accepted that the overwhelming majority of transient blood coagulation defects complicating pregnancy and the puerperium are due to acquired fibrinopenia. A change in the traditional attitude of "watchful expectancy" in the management of missed abortion and dead foetus *in utero* may well be overdue.

Rapid Laboratory Diagnosis of Acquired Fibrinopenia

We now propose to consider the practical laboratory methods for confirming the clinical diagnosis of fibrinopenia. When the scarcity of pure fibrinogen and the excessive cost of quadruple-strength plasma are considered it will be realized that the indiscriminate use of these preparations would not be viewed with equanimity by hospital managers.

Acute defibrination complicating pregnancy is easily recognized in those cases in which the coagulation time is strikingly prolonged. In the Lee and White test the blood does not clot. Unfortunately the coagulation time may remain within normal limits even when a degree of fibrinopenia exists which is of such magnitude that surgical intervention or any active manipulation may prove extremely hazardous for the patient. There is therefore a place for a rapid procedure which will confirm the clinical suspicion of the presence of less severe degrees of fibrinogen depletion. Weiner *et al.* (1950), as we have already pointed out, recommend observation of the coagulum formed in freshly drawn venous blood. Reduction of plasma fibrinogen below a critical level results in a failure of the clot to maintain itself, with dissolution of the coagulum. The normal range of plasma fibrinogen is about 220 to 400 mg. per 100 ml. Higher levels are attained in normal pregnancy as term is approached, reaching about 450 mg. per 100 ml. (range 300–600 mg. during labour). Still higher levels are attained in toxaemic subjects. It appears that when haemorrhage occurs in pregnancy in association with depleted plasma fibrinogen, haemostasis cannot be secured while the level remains below 200 mg. per 100 ml.

Schneider (1952) has described the following method for the rapid assay of plasma fibrinogen. The test does not claim to furnish more than a rough index of the fibrinogen level. In effect it consists of serial dilution of the patient's whole blood with observation of the highest titre in which a discernible fibrin coagulum is formed. The test may be carried out with or without the addition of thrombin. Feeling that the number of variables influencing the result of the test should be reduced when preformed thrombin is added, we have adopted the former method as a routine.

We have used the method extensively, and find it of value in the management of intractable haemorrhage in obstetrics.

Schneider Test

Materials.—Test-tubes, 3 by ½ in. (7.5 by 1.3 cm.), are arranged in a rack, a row of eight tubes being adequate for the performance of a single test.

Diluent.—Ringer's solution may be used, and is recommended in Schneider's original paper, but an alternative solution was also suggested which we have employed in our own laboratory. This consists of a mixture of nine parts of normal saline with one part of M/40 calcium chloride, a solution commonly available in the laboratory for use in one-stage "prothrombin" determinations.

Thrombin Solution.—The thrombin topical preparation of Parke, Davis & Co. is used. A stock solution of strength 200 units per ml. in 50% glycerol is stored in the refrigerator. This may be diluted to 100 units per ml. for use in the test. The stock solution is stable over a long period.

Procedure.—Place 3 ml. of the diluent in the second tube of the series, 4 ml. in the third tube, and 1 ml. in each succeeding tube. Withdraw 1 ml. of venous blood from the patient by means of a tuberculin syringe with suitable needle. The use of a tuberculin syringe offers the advantage that the syringe can be introduced directly into the tubes containing the diluent solution. Discharge 0.5 ml. of blood immediately into the first (dry) tube. The remaining 0.5 ml. is added to the 3 ml. of diluent in the second tube. After thorough mixing, 1 ml. of the mixture is withdrawn and added to the 4 ml. of diluent in the next tube. The process is repeated in the case of each succeeding tube, transferring a 1-ml. aliquot in each case. Assuming a haematocrit value of 35 vols.%, the dilutions of plasma represented by the several tubes in the series are 1, 10, 50, 100, 200, 400, 800, and 1,600.

To each tube 0.1 ml. of the thrombin solution (100 units per ml.) is then added. The tubes are shaken sufficiently to ensure adequate mixing. The tubes are then allowed to stand at room temperature.

Reading the Test.—Even when using added thrombin we have found it advisable to wait an hour before reporting on the highest titre in which a discernible fibrin coagulum is formed, but a result accurate enough for clinical guidance will be available after 15 minutes.

We have not encountered any normal pregnant patient with a Schneider titre lower than 1 in 200, and it is suggested that failure to form a well-defined coagulum in a titre of 1 in 100 or in any lower dilution may be accepted as a pointer towards the necessity for replenishment of the patient's reserve of plasma fibrinogen.

Since the objection has been raised that the Schneider assay does not bear a true relation to plasma fibrinogen level we compared the results obtained by the Schneider method with the actual plasma fibrinogen level in a short series of normal and abnormal cases (18 patients). The results are stated in Table I.

TABLE I.—*Range of Plasma Fibrinogen (Shea's Method) in Relation to Schneider Titre*

Schneider titres (No. of observations in brackets)	1:100 (3)	1:200 (5)	1:400 (8)	1:800 (2)
Plasma fibrinogen (mg./100 ml.)	62–100	120–225	150–300	200–300

The comparative figures in three cases in which fibrinopenia was suspected are of interest (Table II). The titre 50–100 implies good coagulum formation at a dilution of 1 in 50 with very weak coagulum at 1 in 100.

TABLE II.—*Comparative Schneider Titre and Plasma Fibrinogen Level*

Clinical State	Schneider Titre (Pre-transfusion)	Plasma Fibrinogen (Same Sample)
Abruptio placentae	50–100	100 mg./100 ml.
,, ,, ...	50–100	90 ,,
Missed abortion	50–100	62 ,,

The two cases in Table III illustrate the behaviour of the Schneider titre over a period of 24 hours after admission to hospital with intractable bleeding due to abruptio placentae.

TABLE III.—*Serial Schneider Assays in Two Cases of Intractable Accidental Haemorrhage*

Hours after Admission:	0	4	8	20	24
Case A	100	100	100–200	200–400	—
,, B	10	—	50	—	200

Rapid Fibrinogen Estimation

The need for a simple and rapid method for the estimation of plasma fibrinogen has become acute. The most convenient methods depend on colorimetric estimation, using a phenol reagent or a biuret reagent, but few are both rapid and easy to use. Of the methods using a phenol reagent, one of the most practical is that described by Quick (1951). One of us has introduced a biuret method which can be carried out rapidly and conveniently in any small laboratory (Shea, 1954). While for analytical accuracy 90 minutes are required with this method for the estimation, a 90% recovery of fibrinogen can be secured in about 10 minutes, and the fibrinogen estimated in a further 30 minutes. In emergency, accuracy of this order is more than sufficient as a guide to

clinical treatment. The following is an account of the practical details of this biuret method for fibrinogen estimation :

Reagent:

Sodium potassium tartrate ..	9 g.
$CuSO_4.5H_2O$	3 g.
Potassium iodide	5 g.
0.1 N NaOH	to 1 litre
Distilled water	to 1.9 litres

Thrombin Solution:

P.D. & Co. thrombin topical in 50% glycerol-saline.

Procedure.—Take blood in the Heller–Paul (Wintrobe) oxalate mixture. If possible secure 3 ml. of plasma. Add 20 units of thrombin per ml. of plasma. Clotting should occur within about 5 seconds, and rapidly even at 5° C. Provided that the plasma clots within 60 seconds, upwards of 97% of the fibrinogen will be precipitated in one hour, even if clotting occurs and is allowed to continue at a temperature as low as 5° C. After one hour at 5° C. or 37° C. the clot is spilled out on to a filter paper or a paper towel (preferable) and the plasma expressed in three or more stages. The clot is washed in distilled water, and the fluid again expressed. The clot is then transferred to a boiling-tube containing 0.5 ml. N NaOH, and dissolved by heating in a boiling-water bath for two to three minutes. Then 9.5 ml. of the biuret reagent is added and the colour developed by heating in a water-bath at 30–32° C. for 30 minutes. A reagent blank is prepared by the addition of 9.5 ml. of the reagent to 0.5 ml. N NaOH with similar incubation at 30° C. for 30 minutes. The optical density of the test is read against the reagent blank in a photo-electric colorimeter at 555 μ, each tube being at about 30° C. The instrument is calibrated by duplicate estimations by the Kjeldahl method. The reagent described gives a colour which follows Beer's law.

Summary

Two methods of confirming the clinical diagnosis of acquired fibrinopenia in pregnancy are described. Patients who show a Schneider titre of 1 in 100 or less (plasma fibrinogen probably below 120 mg.) should be regarded as potential victims of a haemorrhagic diathesis. If haemorrhage occurs it cannot be checked without restoring the blood fibrinogen. Even if there is no manifest haemorrhage, disastrous bleeding may be provoked by active intervention. Since stored blood for transfusion will have a fibrinogen content of 200 mg. per 100 ml. or less, it may not be possible to raise the blood fibrinogen to a safe level by transfusion of whole blood. If pure fibrinogen is not available a rapid restoration of clotting power may be achieved by the intravenous injection of triple- or quadruple-strength plasma (1 pint (570 ml.) of quadruple-strength plasma yields about 4.4 g. of fibrinogen).

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The British Red Cross Society's report for the year 1954 has just been published. It contains information about the various activities undertaken by the British Red Cross Society, such as first-aid and ambulance work, nursing, blood transfusion, welfare, and the administration of auxiliary hospitals, homes, and settlements. Some of the homes for old people established by the Society are for permanent residents, while others receive short-stay guests. The report states that the demand for the latter type of accommodation is increasing.

BLOOD COAGULATION FAILURE IN OBSTETRICS

EFFECTS OF DEXTRAN AND PLASMA

BY

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In the course of a study of coagulation failure associated with hypofibrinogenaemia in obstetrics (to be reported in detail elsewhere), a review was carried out of maternal deaths, and of cases of accidental ante-partum haemorrhage, among 85,000 deliveries in the practice of certain hospitals in Birmingham, Liverpool, and London between 1937 and 1955. Eight cases of coagulation failure were discovered, seven of them serious and four being fatal. In five the condition complicated accidental ante-partum haemorrhage. One of the most interesting findings of the inquiry was that only one of the cases occurred prior to 1951, the remainder being encountered during the period 1951–5. This is in keeping with the fact that, although coagulation failure in association with accidental haemorrhage was described as early as 1901 (De Lee), very few instances were recorded until the present decade, while the last few years have seen a spate of case reports and articles on the subject in medical journals throughout the world.

There seems little doubt that the recent increase in the incidence and clinical importance of this problem is real and not apparent, and consideration of the available evidence suggests that the most likely explanation for it is the introduction and widespread use of artificial macro-molecular substitutes for blood and plasma. In this country the most popular preparation of this kind is dextran,* and it is remarkable that it is only since it was widely adopted about five years ago that cases of afibrinogenaemia have been relatively common. Moreover, in six of the seven cases mentioned above which occurred during the 1951–5 period, dextran was transfused in comparatively large amounts—the average amount per case was a little more than 3½ pints (2 litres)—and most of it was given before there was evidence of the blood failing to clot. In the seventh case, failure of the blood to coagulate was a transient phenomenon which disappeared quickly, without causing serious anxiety, when 2 pints (1.1 litres) of whole blood was transfused. Moreover, in one of the above cases serial haematological studies revealed a striking deterioration in the quality of the clot formation within a period of 15 minutes during which 1 pint (570 ml.) of dextran was administered. In another of our patients 5 pints (2.8 litres) of dextran was given as part of the treatment of atonic post-partum haemorrhage, and this appeared to precipitate coagulation failure, which had not been present previously. The clotting function in this case was not properly restored until 12 hours later, by which time 6 pints (3.4 litres) of blood had been transfused.

These observations receive support from the published accounts of other cases. McKay *et al.* (1955) described a case in which coagulation failure developed rapidly after

*Dextran is a complex polysaccharide of large and variable molecular size. Commercial preparations vary, but in the one used in most of these cases 63% of the molecules fell within the weight range of 130,000–250,000. It was administered as a 6% solution in normal saline.

the administration of dextran, the basic coagulation defect being hypofibrinogenaemia, while Soulier *et al.* (1952) and Lepage *et al.* (1952) describe cases which followed the administration of polyvinylpyrrolidone, a similar type of large molecular plasma substitute. Hodgkinson *et al.* (1955), in a recent extensive review of coagulation defects in obstetrics, has also commented on the possible association between the coagulation disorder and the use of "plasma expanders" of the dextran type.

Apart from clinical data such as the above, there is experimental evidence to support the conjecture that dextran can exercise an adverse effect on the coagulation mechanism, and this is discussed later.

Mechanism of the Coagulation Disorder

The coagulation disorder occurring in obstetric patients is now generally accepted as being the biphasic one suggested by Schneider (1951, 1952a), and it is illustrated diagrammatically in Fig. 1. An initial state of increased coagulability (*Phase I*) is induced by the release of thromboplastic material into the general circulation from the placental site or as a liquor amnii. This leads to precipitation of fibrinogen as fibrin, which forms multiple tiny emboli in the pulmonary and other capillary beds. In certain cases the plugging of the blood vessels may lead to focal areas of

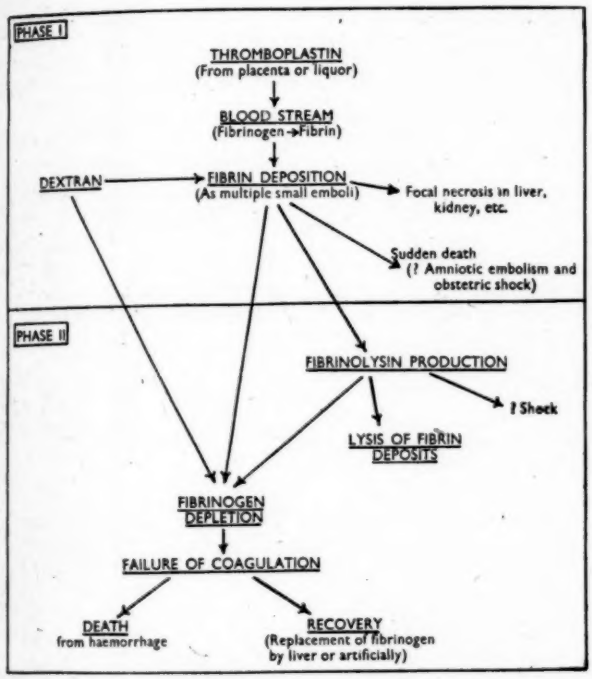

FIG. 1.—Mechanism of coagulation disorder.

necrosis in various organs (McKay *et al.*, 1953) and, if very extensive, can cause sudden death. Deposition of fibrin, and possibly fibrinolysis (or fibrinogenolysis), leads to a depletion of circulating fibrinogen which, if sufficiently severe, results in failure of blood clotting (*Phase II*).

There seems little doubt that the end-result of the process, and the main factor in the coagulation failure, is severe hypofibrinogenaemia (or afibrinogenaemia), although the mechanism may not be precisely as postulated, and other agents such as Factor V (accelerator globulin) may be secondarily involved.

The level of fibrinogen in the blood of normal women in labour at term, according to our observations, averages 0.45 g.% (range 0.35–0.55 g.), but this can be reduced to as low as 0.1 g.% in cases of abruptio placentae without the patient showing clinical evidence of coagulation failure. The critical level at which coagulation fails and at which uncontrollable haemorrhage is liable to occur is between 0.07 and 0.1 g.%.

Effect of Dextran

Ricketts (1952) and Fletcher *et al.* (1952) showed by *in vitro* experiments with fibrinogen solutions that, under certain conditions, dextran can react with and inactivate fibrinogen by forming a dextran–fibrinogen compound which may precipitate. However, since only 10% of the fibrinogen was involved in this reaction, these workers concluded that it was unlikely to be of clinical significance. Laurell (1951), as a result of experiments on rabbits, attributed a "fibrinoplastic" action to dextran whereby it encourages the formation of fibrin from fibrinogen, especially when the molecular weight averages 75,000. Adant (1954), working with dogs, showed a decrease in fibrinogen levels following dextran infusion, and concluded that the initial fall is the result of haemodilution but that a second fall has another mechanism. The levels were rapidly re-established in the intact but not in the hepatectomized animal. Carbone *et al.* (1954) recorded haemorrhagic manifestations in two patients treated with large quantities of dextran, and, in experiments on human subjects, demonstrated a decrease in the fibrinogen levels following dextran infusions.

There is therefore considerable clinical and experimental evidence to show that dextran can exert an unfavourable action on the coagulation mechanism. By itself this may not often be sufficient to result in clinical manifestations of coagulation failure, but in the patient already suffering from hypofibrinogenaemia (as are approximately 30% of patients with moderate or severe accidental ante-partum haemorrhage) it may be enough to tip the scales, converting a subclinical blood change into a state of uncontrollable bleeding.

Dextran exerts this effect (*a*) by simple dilution of the already decreased fibrinogen content, and (*b*) by encouraging precipitation of fibrinogen as fibrin or forming a fibrinogen–dextran compound and thus acting as a contributory factor to *Phase I* of the coagulation disorder (see Fig. 1). The second effect is possibly not operative in all cases, its occurrence probably depending on (*a*) the relative concentrations of dextran and fibrinogen, and (*b*) the molecular weight of the dextran employed.

Effects of Plasma

Prior to the introduction of dextran, most patients in urgent need of blood-volume restoration received plasma transfusions pending the availability of compatible blood. The fibrinogen content of plasma is high, even when stored for long periods. Samples prepared by reconstitution of dried plasma which had been stored at room temperature for three years were found to contain an average of 0.35 g.% of fibrinogen. Thus, unlike dextran, plasma transfusion helps to restore the fibrinogen level to normal. The increased incidence of afibrinogenaemia and of hypofibrinogenaemia severe enough to cause serious haemorrhage coincides with the decreased use of plasma which came about a few years ago.

Plasma transfusions fell from favour because of the considerable risk of hepatitis which was noted, particularly during the war years, when "large pool" plasma was used. In recent years "small pool" plasma has replaced the older type preparations, and Lehane *et al.* (1949) showed that with this the risk of hepatitis is no greater than when whole blood is used. Stored citrated blood also retains much of its original fibrinogen content, and estimations performed on blood stored for 8 to 16 days show an average level of 0.29 g.%.

Recognition of Hypofibrinogenaemia

The persistent escape of incoagulable blood from the placental site or from obstetrical and surgical wounds provides obvious clinical evidence of the final stage of the blood disturbance. It is clearly desirable, however, to have

means of recognizing fibrinogen depletion before it reaches a dangerous level, especially as we have evidence that such a level can be present for some time before frank haemorrhage develops.

In the course of our investigations the fibrinogen content of blood was estimated, using the micro-Kjeldahl distillation apparatus. This method takes several hours, so it is obviously of little practical value. Other less accurate methods, such as serial dilution clotting (Schneider, 1952b), clot observation (Weiner *et al.*, 1950), micro-electrophoresis (Barnett and Cussen, 1954), and the Shea colorimetric method (Barry *et al.*, 1955), are described, but none of these are rapid enough, nor can they be easily performed at the bedside.

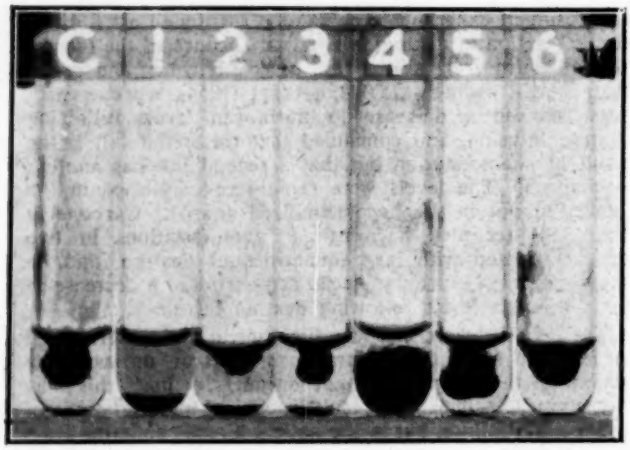

FIG. 2.—Rapid fibrinogen assays in case of abruptio placentae. (See key.)

A modified form of the test recently described in the advertisement of "fibrindex"* was found to be an eminently practical if rough method for assaying fibrinogen in the delivery room. To 0.2 ml. of citrated blood in a small test-tube is added 0.2 ml. of thrombin solution, freshly prepared by dissolving 50 N.I.H. units of dried thrombin in 1 ml. of saline, both these being obtainable in ampoules. If the fibrinogen level is normal, clotting is evident within 5–10 seconds and the clot is firm and stable at 60 seconds. Thereafter it contracts with the extrusion of serum. Delay of the initial clotting beyond 15–20 seconds and liquefaction or disintegration of most of the clot at 60 seconds indicate that the fibrinogen level is considerably reduced, while absence of clot formation during 60 seconds is evidence of afibrinogenaemia. The interpretation of the test is greatly facilitated for the occasional user by setting up a control tube with blood from a normal patient; the amount of thrombin solution prepared allows for this. The great advantage of this method is that a result is obtained within one minute, and this can be vital in certain circumstances.

*This is not at present available in the United Kingdom. The thrombin used was prepared by S. Maw Son and Sons, Ltd.

Fig. 2 gives a photographic illustration of a series of tests performed by this method during the course of an accidental ante-partum haemorrhage.

Treatment of Hypofibrinogenaemia

1. *Preventive.*—Hypofibrinogenaemia is demonstrable in 30–40% of cases of severe or moderately severe accidental ante-partum haemorrhage, but it is rarely of such a degree as to manifest itself clinically. Further lowering of the fibrinogen level to the extent of making the blood incoagulable is avoided by: (*a*) Reduction of intrauterine pressure by early rupture of the membranes, thus diminishing the risk of absorption of thromboplastin from the placenta into the maternal circulation. (*b*) The encouragement of rapid delivery for the same reason. Rupture of the forewaters helps to achieve this but it also raises the question of the places of oxytocin and caesarean section; these and other obstetrical considerations are outside the scope of this communication. (*c*) The avoidance of dextran or other similar artificial blood substitutes; emergency transfusion should be with "small pool" plasma if blood is not immediately available.

2. *Curative.*—If coagulation failure does develop, fibrinogen replacement is urgently indicated. This can be achieved by transfusion of the fibrinogen fraction isolated from human plasma (Weiner *et al.*, 1950). Reid *et al.* (1953) recommend a dose of 8–12 g., but there would seem to be no necessity to give more than is required to restore blood-clotting. This can be sometimes achieved by very small amounts, Barnett and Cussen (1954) having been successful with less than 0.5 g. in two cases. Fibrinogen preparations, however, are in short supply in this country, although they may be obtainable from Regional Transfusion Centres. An excellent substitute is nevertheless readily available in most maternity units—namely, dried plasma ("total plasma solids": Barry *et al.*, 1955). If this is reconstituted to double strength by simply adding half the usual volume of water—that is, 200 ml.—it provides a solution containing approximately 0.7 g.% of fibrinogen, and 1 to 2 pints (0.5 to 1 litre) of this should be sufficient to correct afibrinogenaemia in the majority of cases. Indeed, it appears doubtful if there is any advantage in using the fibrinogen fraction, because it carries the same hepatitis risk as does plasma, and the latter may in addition contribute other coagulation factors.

KEY TO FIG. 2

Tube		C	1	2	3	4	5	6
Specimen		Normal control	Patient's 7 a.m.	8 a.m.	9 a.m.	10 a.m.	11.50 a.m.	2 p.m.
Rapid test results	Initial clot	7 secs.	15 secs.	15 secs.	10 secs.	10 secs.	10 secs.	8 secs.
	At 60 secs.	Stable clot	Poor clot serum ++	Poor clot serum +	Stable clot	Stable clot	Stable clot	Stable clot
	At 1 hour	Normal clot	Clot dissolved	Clot partially dissolved	Almost normal clot	Normal clot	Normal clot	Normal clot
Fibrinogen level (micro-Kjeldahl) g. %		0·350	0·175	0·237	0·237	Specimen clotted	0·306	0·237
Fibrinolytic activity		Nil	79%	13%	26%	,, ,,	14%	8%
Treatment and progress				Plasma ½ pint A.R.M.	Blood ½ pint	Blood ½ pint	Delivery. Blood 1 pint	—

Hypofibrinogenaemia in Conditions Other than Abruptio Placentae

It should here be mentioned that although afibrinogenaemia occurs most commonly as a complication of accidental ante-partum haemorrhage it is also reported in association with abortion, hydatidiform mole, intrauterine death of the foetus, amniotic embolism, and tumultuous action of the uterus in labour. The above arguments apply equally to the management of these conditions. Moreover, a similar mechanism may operate in non-obstetric procedures, such as thoracic surgery. The lung is almost as rich in thromboplastin as is the placenta, so its handling at operation may set in train the sequence of blood changes resulting in

afibrinogenaemia (Soulier *et al.*, 1952; Baumann, 1952). It may well be, therefore, that dextran carries a risk in this field, as it does in obstetrics.

Summary

Plasma should be preferred to dextran as an emergency blood-volume restorer in conditions in which hypofibrinogenaemia is apt to develop. The most important of these is accidental ante-partum haemorrhage, others being retention of a dead foetus *in utero*, and hydatidiform mole.

The transfusion of dextran or similar preparation in any circumstance should be limited to 1 to 2 pints (0.5 to 1 litre).

Hypofibrinogenaemia can be recognized quickly by a simple thrombin coagulation test before there is clinical evidence of its presence.

In cases of coagulation failure due to fibrinogen deficiency, transfusion of double-strength plasma offers a readily available method of treatment.

I am indebted to Professor T. N. A. Jeffcoate for a great deal of patient criticism and advice. I have to thank Colonel B. Blewitt, Dr. G. Alun Roberts, and Mr. G. Williamson for fibrinogen estimations performed in Newsham General Hospital Laboratory. Dr. D. Lehane kindly made available supplies of plasma. The cases were reviewed by permission of the consultant obstetric staff of Birmingham Maternity Hospital; Queen Charlotte's Hospital, London; Liverpool Maternity Hospital; and Mill Road Maternity Hospital, Liverpool.

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In 1951 the London County Council decided to improve the main drainage works at Northern Outfall, which were constructed in 1864 as part of the Metropolitan Board of Works scheme for the collection and disposal of sewage. The new construction is to ensure the adequate treatment of sewage, and is the council's contribution to the improvement of the quality of Thames water, which has deteriorated recently. Work at present in hand, or proposed, includes the finishing of the detritus pits started before the war; the construction of primary sedimentation channels to treat up to 200 million gallons (909 million litres) per day; sludge digestion plants to treat up to 4,000 tons (4 million kg.) of sludge per day; and a diffused air plant to treat an additional 60 million gallons (273 million litres) of sewage effluent per day. The total cost is estimated to be about £8,465,000. The whole of the sludge produced will be digested, and 2½ million cubic feet (70,000 cubic metres) of methane gas will be available as power for driving the eight 960-horse-power gas turbines to be installed in the power house. By the end of 1957 these works should be operating and the condition of the effluent discharged into the river made satisfactory at all times.

USE OF CORTICOTROPHIN GEL AND CORTISONE IN TREATMENT OF SEVERE AND INTRACTABLE ASTHMA

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In the same year as Hench *et al.* (1949) reported the dramatic effect that cortisone produced in rheumatoid arthritis, Bordley *et al.* (1949) reported the "unequivocal benefit within 4–48 hours" that five chronic asthmatics derived from injections of corticotrophin. Since 1949 there have been many reports from abroad (including Carey *et al.*, 1950; Rose *et al.*, 1951; Schwartz, 1951; Shulman *et al.*, 1951; Baldwin and de Gara, 1952; Arbesman *et al.*, 1952; Baldwin *et al.*, 1955), and a few from this country (Ball, 1954; Savidge and Brockbank, 1954; Pearson, 1955), confirming the striking, though temporary, relief that can be obtained in the large majority of cases of otherwise intractable asthma with short courses of corticotrophin or cortisone.

Gay and Murgatroyd (1954) reported favourably on their results with corticotrophin gel in 76 patients. They gave only one injection a day, and emphasized the value of this therapy in "ambulatory" patients, thus avoiding the cost of hospital admission.

Long-term continuous therapy with these hormones is also being reported, and indications are that continued relief can be obtained (Baldwin *et al.*, 1955).

There are contraindications to the use of these hormones, and some cases of asthma do not respond. Furthermore, the relief produced is only temporary, symptoms recurring soon after the treatment is stopped. It is the main purpose of this article to measure the results of short-term therapy with cortisone, corticotrophin, and hydrocortisone in cases of severe and/or intractable asthma.

Material and Methods

Our observations are based on 63 courses of treatment on 50 adult patients—44 asthmatics (Table I) and 6 chronic bronchitics with persistent wheezing. The six chronic bronchitics were all male, their ages ranging from 37 to 66 years.

TABLE I.—*Data on the* 44 *Asthmatics*

	Sex		Present Age		Type of Asthma	
	Male	Female	Under 40 Years	40+ Years	Extrinsic	Intrinsic
No. of cases	12 (27·3%)	32 (72·7%)	9 (20·5%)	35 (79·5%)	2 (4·5%)	42 (95·5%)

The youngest was aged 17, two were over 70.

Twenty of the patients were treated by Dr. Leslie Gay, of the Johns Hopkins Hospital, when he visited Cardiff in June, 1954, bringing with him supplies of corticotrophin gel and hydrocortisone. As requested by Dr. Gay, they were patients whose asthma had been intractable to all previous therapy; 10 were treated as out-patients and 10 as in-patients. The remaining 30 were treated in hospital, and whether corticotrophin or cortisone was used depended mainly on its availability.

Before treatment was started a careful history of the patient was taken and physical examination made: all had radiographs of the chest and sinuses, all asthmatics were skin-tested, most had electrocardiograms taken, and daily vital capacity estimations and eosinophil counts were made.

Before it was decided whether or not to use cortisone or corticotrophin, each patient was specifically asked if he or she had had a peptic ulcer or if there had been any dyspepsia at all. Peptic ulceration is a definite contraindication to the use of these hormones, and a few cases were excluded because of recent duodenal ulceration. One patient who had had a proved duodenal ulceration sixteen years previously but no symptoms since was included. Inquiry and examination were also made regarding a "nervous breakdown," diabetes, tuberculosis, and hypertension, but no patient was excluded on these grounds.

Eleven of the asthmatics were having very severe attacks, and were treated within twenty-four hours of admission to hospital, having failed to respond to subcutaneous adrenaline and intravenous aminophylline. The other 33 were of the chronic intractable type, and had failed to respond to a reasonable period of antispasmodics, antibiotics, sedation, and breathing exercises.

Corticotrophin gel was used alone in 27 courses of treatment, in one case a course of corticotrophin only was given, and in 17 courses cortisone was used alone. Corticotrophin gel was given and followed by hydrocortisone tablets in 15 courses and corticotrophin gel was followed by cortisone in three.

The corticotrophin gel was given deeply intramuscularly with a *dry syringe* and a 20-gauge needle. The gel was liquefied by standing in warm water or by being held in the hand, and no difficulty was experienced in giving it, nor did the patients complain of any untoward pain. Dr. Gay used 60 to 100 units on the first day, depending on the severity of the symptoms; 60 to 80 units on the second and third days; 20 to 60 units on the fourth and subsequent two or three days, depending entirely on the individual response; followed by hydrocortisone for six to twenty days. In general, on the chronic intractable in-patients we used 80 units daily for four days, followed by 40 units for three days.

The dose of cortisone used in status asthmaticus was 300 mg. in divided doses on the first day, 200 mg. on the second day, and 100 mg. on the third day. This dose was repeated on subsequent days or reduced according to the patient's progress. In chronic intractable asthma the usual dose was 100 mg. a day for four days, followed by 75 mg. a day for three days. If the initial dose of 100 mg. was not effective 300 mg. was usually given for a few days. As symptoms subsided so dosage was lowered until the chest had been clear for a few days. In the main, treatment was continued for seven to fourteen days.

In addition to these hormones, a mixture containing 2 g. of potassium acetate in each ½ oz. (14 g.) was given three times a day and a diet low in sodium with added vitamin C. When hormone treatment was started in-patients continued with physiotherapy and some with antibiotics. All were allowed to use antispasmodic measures, inhalers, or tablets as required, and their use was noted.

The diagnosis of asthma was made mainly on the history of recurrent attacks of spontaneous dyspnoea and wheeziness. Chronic bronchitis was diagnosed in those patients who had persistent wheeziness but no spontaneous paroxysms of dyspnoea. This differentiation is sometimes difficult, but in view of the essential differences in their pathology (Gough, 1955) and their apparent differences in response to hormonal therapy it is clearly important. The classification into intrinsic and extrinsic asthma (Rackemann, 1940) was made because of its general acceptance and because of the difficulties in assessing the relative importance of the infective and psychological factors which are the dominant factors in the majority of chronic asthmatics. Assessment of progress was made daily. Our results were recorded as good, fair, and poor. "Good" meant complete subjective relief with complete, or nearly complete, clearing of the chest of adventitious sounds; "fair" and "poor" meant some and no improvement respectively. When the patients left hospital they were seen weekly at the asthma clinics.

Results in Asthmatics

The results of 56 courses of treatment in 44 asthmatics are shown in Table II.

TABLE II.—*Table of Results in Asthma*

	Good	Fair	Poor	Deaths	Total
No. of courses ..	49 (87·5%)	3 (5·3%)	3 (5·3%)	1 (1·8%)	56

Death.—One patient died in this series—a woman of 53 who was admitted with severe intractable asthma and was treated with antibiotics and antispasmodics for thirty days. Her condition deteriorated, and she was then given daily 300 mg., 200 mg., 100 mg., and 100 mg. of cortisone, when she died. At necropsy the typical findings in death from asthma—widespread plugging of the bronchi—were present. It is clear that death was due to failure to relieve her asthma, and not to the cortisone itself.

Poor Results.—The three poor results occurred in two women and one man. The man, aged 54, failed to respond after 625 mg. of cortisone over seven days with a maximum daily dose of 100 mg. Six days later he was given corticotrophin gel with a good response. One woman, aged 71, failed to respond after 450 units of corticotrophin gel with a maximum daily dose of 75 units. A week later her chest cleared after a course of oxytetracycline ("terramycin"). The second woman, aged 38, failed to respond to 475 units of corticotrophin gel over five days with a maximum daily dose of 75 units, followed by 1,200 mg. of cortisone over eight days, with a maximum daily dose of 300 mg., although she had a marked fall of eosinophils. Treatment was stopped on account of calf-vein thrombosis and pulmonary embolism. She was continued on antibiotics, and in four weeks her chest cleared. All three cases had a heavy purulent sputum.

Fair Results.—Only fair results were obtained in three courses. One of these was due to the use of 10 units of corticotrophin gel daily for five days, a dose which was obviously too small. The other two fair results both occurred in a woman of 62 years who had had many months of intractable asthma. On the first admission, after having 450 units of corticotrophin gel with a maximum daily dose of 75 units over seven days (after a previous week of antibiotic treatment), there was only slight improvement. On her second admission, in status asthmaticus, she responded well to cortisone. On her third admission, a month later, she again had only a fair response to corticotrophin gel, 600 units given over eight days with a maximum dose of 75 units. At this time a right middle-lobe collapse was present, and the sputum was heavily purulent.

Good Results.—Good results were obtained in the two extrinsic asthmatics and in the remaining intrinsic cases. The improvement in the out-patients under Dr. Gay's treatment was very striking: one of his patients had to be wheeled into the clinic on account of a severe exacerbation of her asthma, and her response without hospital admission was an excellent example of what Dr. Gay has emphasized. With the in-patients, the reduction of their period of disability compared with that previously experienced with chronic asthmatics was also most striking. We no longer have our beds held up for weeks or months with several cases of intractable asthma. This is apart from the relief experienced by the patients. The assessment of the cases of status asthmaticus in this group is more difficult, but all cases had failed to respond to adrenaline and adequate doses of intravenous aminophylline, and hormonal treatment appeared to us to be life-saving in many cases.

Results in Chronic Wheezy Bronchitis

Our cases of wheezy bronchitis are too few for any conclusions to be drawn on the effect of hormonal therapy in chronic bronchitis, but it would appear that there was an essential difference between the response of asthmatics as a group and the chronic bronchitics. Our bronchitis cases were given similar treatment to the asthmatics, yet in only two were the results good (Table III). In neither of these was the relief as dramatic as was usual with the asthmatics.

TABLE III.—*Results in Chronic Bronchitis*

Males	Average Age	Courses of Treatment	Results		
			Good	Fair	Poor
6	56	7	2	3	3

TABLE IV.—*Complications of Treatment (Excluding the One Death)*

	None	Slight	Severe	Doubtful	Total
No. of courses ..	46 (74·2%)	10 (15·9%)	3 (4·8%)	1	60

Complications (Table IV)

A moderately severe melaena occurred in a man of 66 years with a proved duodenal ulcer sixteen years ago when he had had a barium meal examination, but who had had no gastric symptoms since. Two patients had severe and painful furunculosis.

The case classed as doubtful was that of a woman of 38. She developed a pulmonary infarction and calf-vein thrombosis (previously mentioned) after six weeks in bed, and so cortisone cannot definitely be incriminated, despite its known influence on blood-clotting mechanisms (Chatterjea and Salomon, 1954).

Five patients developed varying degrees of oedema, but in none was it severe, and all cleared rapidly, mercurial diuretics being used in three. A slight hypertension occurred in two patients, one of them having a transient glycosuria, while another patient also developed a transient glycosuria. "Moonface" and slight euphoria occurred in two patients.

There is general agreement that, when these hormones are given in properly selected cases for short periods, side-effects are infrequent and relatively mild. Constant care, however, is necessary.

Periods of Remission

The periods of remission varied from one day to 240 days, with an average of 30.3 days.

The results following 42 courses are given in Table V. It will be seen that 43% had over three weeks' complete remission of symptoms. The natural remissions which occurred in our two seasonal asthmatics have not been included: the remissions during the season, which occurred on terminating therapy, were of two days and seven days. The more severe of the two was then given further hormone therapy to the end of the season, with good results.

TABLE V.—*Duration of Remission of Asthma after 42 Courses*

Length of Remission	No.	%		
Less than 3 days	3	7		
3–10 days	13	31		
11–20 days	8	19		
21 days to 5 weeks	10	24		
5 weeks to 8 weeks	2	5	19	43
Over 2 months	6	14		

Average period of remission, 30·3 days. Maximum period of remission, 240 days.

A later follow-up between three and ten months after the 41 asthmatics had had their last course gave these findings: 6 (15%) have had very little asthma since; 16 (39%) have had varying degrees of moderately severe asthma, necessitating supervision at the clinic; 8 (20%) have had moderately severe, in some cases severe, asthma hardly controlled by the clinic therapy (if supplies of the hormones had been more easily obtainable they would have had continuous therapy); 11 (26%) were receiving maintenance therapy.

Thus, of these cases of severe asthma, 19 (46%) would ideally require the use of more continuous therapy. These are, of course, only a very small proportion of those attending the asthma clinics: our figures suggest such a requirement in 1 in 80 to 1 in 100 of adult clinic patients.

Dosage of Corticotrophin Gel and Cortisone

Bayliss and Steinbeck (1954), in estimating the plasma steroid level after corticotrophin gel injections, noted that the response varied in different patients and that 20 or 80 units might in different patients raise the plasma steroids to the same level. They found no constant elevation of the plasma steroids twenty-four hours after corticotrophin gel, but, with Gay and Murgatroyd (1954), we have found one injection a day to be sufficient in chronic intractable asthma.

As already indicated, we have found the dose required varies with the severity of the asthma, 100 to 60 units of corticotrophin gel on the first day, 80 to 60 units on the second day, etc., and that for the average intractable asthmatic in hospital, a suitable basis for dosage is 80 units daily for four days, followed by 40 units for three days.

Baldwin *et al.* (1955), in very severe asthma, used 40 units every four hours for twenty-four hours (240 units), reducing the dose with improvement to six-hourly, then eight-hourly, and within the week the patients were well on 40 units twice daily; the dosage was then reduced to once a day. They found 40 units daily usually sufficient for the ambulatory intractable asthmatic. With cortisone, also, they recommend larger doses than we have used for severely ill asthmatics—that is, 100 mg. every four hours for the first twenty-four hours (600 mg.)—and state that within a week patients are doing well on 25 mg. three or four times a day. For the intractable case their initial dose of 100 mg. a day is the same as ours. Our dose of 25 mg. four times a day for four days, followed by 25 mg. three times a day for three days, was effective in the average intractable case, although a few needed 300 mg. a day for a few days.

Dosage schemes, however, are not to be laid down by rule of thumb, but should depend on the severity of the asthma and on the patient's response. Symptomatic relief and eosinopenia do not go hand in hand, and present laboratory tests are of little value in guiding dosage.

In the recent literature it is generally agreed that whether the asthma is dominantly allergic, psychological, or infective does not affect its response. Both our extrinsic (allergic) cases responded well, as did the large majority of our intrinsic cases. It was our finding, in common with other workers, that a patient found intractable during one course might respond to a later course. In some of our cases this could have been accounted for by differences in dosage, but not invariably so.

Bickerman and Barach (1954) found that corticotrophin was generally more effective than cortisone and that hydrocortisone was superior to both. Our experiences are too limited to warrant a definite statement, but we have the impression that, in the dosage we used, corticotrophin gel was generally more effective than cortisone. However, deaths have been recorded after corticotrophin (Hill and Swinburn, 1954; Bloom and Wolff, 1954), while the convenience of being able to give cortisone by mouth is an advantage.

Immediate Response and Failure to Respond

Gay and Murgatroyd (1954) reported excellent or good results with corticotrophin gel in 82% of 76 severe asthmatics, moderate or fair results in another 5%, and poor

results or failure in 13%. Baldwin *et al.* (1955) reported satisfactory results in 87% of 60 asthmatic patients using corticotrophin gel and/or cortisone. Kania and Schmidt (1954) found that 76.6% of 111 patients were completely relieved. Our good results (87.5%) are very similar. The general agreement that the large majority of chronic intractable asthmatics can be relieved even temporarily is obviously important, as is the relative absence of dangerous complications if care is taken to exclude cases with peptic ulceration and the other conditions mentioned previously.

The general agreement that a small but definite proportion fail to respond to hormonal therapy is a challenge, and is intriguing. The exact mode of action of these hormones is not known, nor are we sure of exactly what is happening in the bronchi when a patient is wheezing. In those patients who die from status asthmaticus and in whom post-mortem examination shows mucous plugging of the bronchi, the inadequacy of the dose or its late administration would appear to be the cause of failure. Analogy with the use of insulin in diabetic coma is perhaps appropriate.

The importance of distinguishing between asthma and bronchitis has already been pointed out, but it may also become important to distinguish between an attack of bronchitis and an attack of asthma in an asthmatic. We were impressed by the failure of response in one of our patients who had a purely purulent sputum, even though there was a marked eosinophilic drop in the blood, and by the fact that her condition later improved on antibiotics and general measures. Possibly the hormones given relieve asthma due to non-purulent obstruction of the bronchi, but fail to relieve the obstruction due to a frankly purulent bronchitis.

Duration of Response and Need for Maintenance Therapy and Dangers of Treatment

It is of interest that in some of our cases there was a long period of comparative freedom after hormone therapy. This may well have been due to the antibiotic therapy and general measures which they had in hospital, or to a natural remission as mentioned by Savidge and Brockbank (1954). Most of our cases were of the infective type, and many had antibiotics before, during, and after hormonal therapy. All writers are agreed that search into the underlying cause of the asthma and its treatment is still essential.

Of equal interest have been the subsequent requirements of our patients. Our estimate that some 40–50% of them might ideally need maintenance therapy is very closely paralleled by the findings of Baldwin *et al.* (1955). Thirty of their original 60 patients required maintenance therapy. Eleven of our patients have had continuous therapy. Complications known to occur on prolonged treatment include decalcification of the skeleton, Cushing's syndrome, increasing weight, secondary infection, and psychosis. Stoner and Whiteley (1954) have shown at necropsy that continuous cortisone therapy results in an atrophic inactive adrenal gland, while corticotrophin therapy leads to an enlarged active gland. Under adverse conditions disuse atrophy might indeed impair the asthmatic's response to "stress"; yet, so far, clinical reports indicate that this atrophy is reversible (Englemann *et al.*, 1953; Irwin *et al.*, 1954). Savidge and Brockbank (1954) have drawn attention to deaths from asthma that occurred while patients were on continuous cortisone therapy; they believe that the suppression of spontaneous adrenal activity by cortisone therapy might have been partly responsible for these deaths. This possibility must, of course, be considered. We must not, however, forget that deaths from status asthmaticus occur in approximately 3,000 patients each year in England and Wales (Williams, 1953).

Continuous hormonal therapy is beset with known and even possibly unknown risks and needs very careful supervision. We find the smallest dose of cortisone (generally 12.5 to 75 mg. a day) that will keep the patient moderately comfortable with the help also of antispasmodics and not necessarily free from all symptoms. In addition we give corticotrophin gel, 20 units twice a week (Gottlieb, 1954). Any superadded chest infection is immediately treated with antibiotics.

So far we have no cause to regret our use of maintenance therapy, while its effect on our patients has often been most satisfactory.

It is encouraging to read the observations of Baldwin *et al.* (1955) that "in general it may be stated that the longer the hormone therapy is continued the smaller the amount of the drug that is required, if the factors leading to the asthma are progressively treated and managed."

Caution is still, however, very necessary in continuous therapy, but short courses appear to be quite safe if care is taken in the selection of cases.

Summary and Conclusions

The effects of treating 44 chronic asthmatics and 6 chronic bronchitics with 57 and 7 courses respectively of cortisone, corticotrophin gel, and/or hydrocortisone are reported.

Eleven of the asthmatics were in status asthmaticus, the remaining 33 had intractable asthma. In the asthmatics 87.5% of the courses gave good results. The temporary relief afforded lasted on an average thirty days. Continuation of hormonal therapy in these severe and intractable asthmatics was unnecessary in 50% or more, but appeared desirable in some 40 to 50%. Contraindications, complications, and dosage schemes are discussed.

The importance of distinguishing between asthma and bronchitis is emphasized.

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EFFECTS OF METHYLPENTYNOL IN NOCTURNAL ATTACKS OF BRONCHIAL ASTHMA

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In chronic bronchial asthma the symptoms often occur at night-time. Some patients have an attack as soon as they retire to bed; some wake up wheezing and fighting for breath after one or two hours of sleep; and others have an attack early in the morning, making them get up. The symptoms may last a few minutes or a few hours. In any case, the disturbance of sleep brings anxiety to the patient and to his family. Loss of sleep and physical and mental exhaustion render the patient unfit for work or school next morning. Fear of another attack in the approaching night may develop a conditioning reflex, and thus the vicious circle is established.

Hypnotics in Bronchial Asthma

The purpose of hypnotics is to allay nervousness and to induce a natural sleep. Hypnotics in bronchial asthma are very important therapeutic measures, but they should be employed carefully, as some of them may depress the respiratory centre and cough reflex.

Morphine and its derivatives have been condemned by allergists because they depress the respiratory centre. The patient develops anoxia and passes into coma. Bronchial secretions are not coughed up and the patient dies of asphyxia. Recently Mitchell and De Jong (1954) showed that morphine potentiates the effect of acetylcholine on bronchial muscle by inhibiting cholinesterase, and therefore it has a second adverse effect in bronchial asthma.

The Barbiturates.—The patient suffering from nocturnal attacks of asthma due to nervous or psychic causes needs a heavy dose of a barbiturate to induce him to sleep. Such a dose will make him drowsy the next morning. Although there are many barbiturates available for therapeutic purposes, certain dangers are associated with them.

Side-effects of Barbiturates.—It is possible to produce chronic barbiturate intoxication by the frequent taking of these drugs. Mental impairment with changes in the daily habits of the patient, depression, forgetfulness, impaired judgment, carelessness, slow responses, irresponsibility—all of these have been noted by Morgan (1953). He pointed out that these side-effects may mimic organic disease of the central nervous system, such as neoplasm of frontal lobes, or senile dementia. Addiction is common, especially to those with medium action. Allergic manifestations, such as skin rashes, urticaria, or asthma, may develop after taking barbiturates.

Antihistamine Drugs produce a soporific effect, but this wears off after taking them for a few days. They also cause unpleasant side-effects—dryness of the mouth, drowsiness on waking, disorientation, ataxia, headaches.

Pharmacological Action of Methylpentynol

Allen and Krongold (1951) and Margolin *et al.* (1951) published their reports on the action of a new hypnotic which has no barbituric acid in its chemical formula.

Respiratory System.—Methylpentynol (3-methylpentyne-ol-3) does not depress the respiratory centre and has no effect on respiration (Margolin *et al.*, 1951; Allen and Krongold, 1951). It does not exert antispasmodic action (Margolin *et al.*, 1951).

Cardiovascular System and Blood.—Methylpentynol does not alter the pulse rate or blood pressure, and no changes are noted in blood morphology or chemistry after its prolonged administration (Margolin *et al.*, 1951; Allen and Krongold, 1951).

Cerebral Activity.—Tükel and Tükel (1952) studied E.E.G. patterns in children induced to sleep by this drug, and found them to be identical with those of normal physiological sleep. Patients can be easily awakened by sensory stimuli such as pain or noise.

Dosage.—The usual dose is 250 to 500 mg. by mouth, and for children from 1 to 12 years the average effective dose is 150 mg.

Hypnotic Effect.—Hirsh and Orsinger (1952) treated 276 patients with 100 to 500 mg. of methylpentynol and found that 93% of them fell asleep within one hour, and 92% slept for more than five hours.

Side-effects.—No side-effects were observed to follow methylpentynol administration (Allen and Krongold, 1951; Margolin *et al.*, 1951; Tükel and Tükel, 1952).

Contraindications.—There are no contraindications to the administration of this drug. Patients with hepatic, renal, pulmonary, and cardiac disease can take it without harm (Allen and Krongold, 1951; Margolin *et al.*, 1951).

Methylpentynol has been used in patients suffering from various diseases, and as premedication for general and dental anaesthesia. I was not aware if it had been used in chronic bronchial asthma, and therefore decided to carry out a controlled clinical trial in patients suffering from bronchial asthma whose sleep was interrupted by attacks of asthma.

Methods of Observation

Patients suffering from bronchial asthma who complained of frequent nocturnal attacks were selected for the trial. All 15 patients (eight males and seven females) have been fully investigated and were attending the allergy clinic for treatment. Their ages varied from 10 to 73 years.

A control group of 15 patients received inert capsules identical in shape and colour with those of methylpentynol. This series included seven males and eight females. Their ages varied from 12 to 63 years.

The treatment lasted from 6 to 18 months.

Methods of Treatment.—All patients were issued with hospital prescriptions for 250-mg. capsules of methyl-

TABLE I.—*Patients Treated with Methylpentynol*

Case	Sex	Age	Occupation	Duration of Symptoms	Remarks
1	M	53	Labourer	7 years	Wakes up every night between 2 and 3 a.m.
2	F	36	Housewife	19 ,,	Cannot go to sleep because of wheezing
3	M	63	Shipyard foreman	33 ,,	Wakes up at 4 a.m. coughing and wheezing
4	M	73	Retired commercial traveller	58 ,,	Wakes up every night between 1 and 2 a.m.
5	F	43	Housewife	23 ,,	Cannot go to sleep because of wheezing
6	M	56	Labourer	6 ,,	Wakes up coughing and wheezing at 4 a.m.
7	M	43	,,	7 ,,	Cannot go to sleep because of coughing
8	M	63	,,	4 ,,	Cannot go to sleep because of coughing and wheezing
9	M	14	Schoolboy	8 ,,	Cannot go to sleep because afraid of asthmatic attacks
10	M	61	Insurance agent	15 ,,	Cannot go to sleep because of coughing and wheezing
11	F	45	Housewife	4 ,,	Wakes up between 1 and 2 a.m.
12	F	31	,,	5 ,,	Cannot go to sleep because of coughing and wheezing
13	F	38	,,	3 ,,	Is afraid to go off to sleep because of asthmatic attacks
14	F	26	,,	4 ,,	Wakes up every night between 2 and 3 a.m. coughing and wheezing
15	F	10	Schoolgirl	10 ,,	Wakes up every night between 1 and 2 a.m wheezing

pentynol and were instructed to take one before retiring to bed. Two lists were kept at the hospital dispensary—one list with the names of the patients receiving the real drug and the second list with the names of the control series. I did not know which of the patients were receiving the real drug and which were taking the placebo. As the patients were coming every week to the clinic I questioned them about their sleep and the effects of the drug. If necessary the dose was increased. At the end of the trial I prepared a list of the 30 patients, and the hypnotic effect of the drug was estimated for each patient and any remarks made by the patients were noted. Then the chief pharmacist revealed the names of those who were taking the real drug or the placebo. For the sake of clarity I present my clinical observations in Tables I and II.

TABLE II.—*Patients Treated with Placebo*

Case	Sex	Age	Occupation	Duration of Symptoms	Remarks
A	M	49	Baker	30 years	Cannot go to sleep because of wheezing
B	F	63	Housewife	28 ,,	,, ,, ,,
C	F	19	Factory worker	10 ,,	Wakes up every night between 2 and 3 a.m. wheezing
D	F	52	Housewife	8 ,,	Is afraid to go to sleep because of asthmatic attacks
E	F	54	,,	24 ,,	Wakes up between 2 and 3 a.m. wheezing
F	M	23	Labourer	4 ,,	Wakes up between 2 and 3 a.m. coughing and wheezing
G	F	43	Hospital ward maid	24 ,,	Wakes up between 1 and 2 a.m. wheezing
H	M	30	Labourer	7 ,,	Wakes up between 3 and 5 a.m. coughing and wheezing
I	F	38	Cook	31 ,,	Wakes up between 1 and 2 a.m. wheezing
J	F	33	Shop assistant	10 ,,	Wakes up between 2 and 3 a.m. wheezing
K	M	62	Labourer	7 ,,	Wakes up 3 or 4 times at night wheezing and coughing
L	F	17	Paper-mill worker	8 ,,	Wakes up 2 or 3 times at night wheezing
M	M	12	Schoolboy	10 ,,	Wakes up between 1 and 2 a.m. wheezing
N	F	22	Factory worker	18 ,,	Wakes up between 2 and 3 a.m. coughing and wheezing
O	M	52	Labourer	10 ,,	Wakes up 3 or 4 times at night coughing and wheezing

Results of Treatment

Methylpentynol Series.—Table III shows the results of treatment with methylpentynol. One patient (Case 4) slept only occasionally well on 500 mg. of the drug. On closer inquiry it was found that his wife was ill and the worry contributed a great deal to his attacks of asthma. Perhaps if the dose was increased to 750 mg. he would have a regular good sleep. One patient (Case 8) died suddenly during the trial. The post-mortem examination revealed coronary thrombosis. The hypnotic effect of the drug was not estimated for this patient. The rest of the patients claimed that methylpentynol was of great help in promoting a good sleep and abolishing or reducing their nocturnal attacks of asthma. They were not afraid to go off to sleep, and were feeling fresh and strong in the morning and able to face their daily work. One patient (Case 3), whose frequent attacks of asthma at night-time kept him off work the following day, has lost only two days off work in the past 18 months while taking methylpentynol. A schoolboy (Case 9) used to be absent from school several days every term before treatment with methylpentynol, and has lost only 10 days in 12 months while taking the drug. A schoolgirl (Case 15) is suffering from Besnier's prurigo. Frequent attacks of asthma and intense itching of the eczematous lesions kept her awake through the night and made her too exhausted to attend school the next morning. She sleeps well now for eight hours on 250 mg. of methylpentynol, and does not scratch her skin at night-time.

TABLE III.—*Results of Treatment—Methylpentynol Series*

Case	Dose Required	Hypnotic Effect in Hours	Side-effects	Remarks
1	750 mg.	7–8	Nil	Sleeps well and feels fresh in the morning
2	250 ,,	6–7	,,	Goes to sleep easily and feels stronger in the morning
3	500 ,,	8	,,	Sleeps well and feels fresh in the morning
4	500 ,,	4–8	,,	Sometimes he sleeps well; at times no effect
5	500 ,,	7	,,	Goes to sleep easily and feels better in the morning
6	500 ,,	6–8	,,	Sleeps well and feels fresh in the morning
7	250 ,,	8	,,	Goes to sleep easily
8	500 ,,	Nil	,,	Died suddenly (coronary thrombosis)
9	250 ,,	8	,,	Goes to sleep easily within 15 minutes of taking the drug
10	500 ,,	6–8	,,	Goes to sleep easily
11	250 ,,	7	,,	Sleeps well
12	250 ,,	6–8	,,	Goes to sleep easily
13	250 ,,	7	,,	,, ,, ,,
14	250 ,,	6	,,	Sleeps well now
15	250 ,,	8	,,	Sleeps well now and does not scratch the eczematous lesions

Placebo Series.—Table IV illustrates the results of treatment with placebo. Only one patient (Case B) slept well.

TABLE IV.—*Results of Treatment—Placebo Series*

Case	Dose Given	Hypnotic Effect	Side-effects	Remarks
A	750 mg.	Nil	Nil	No difference in sleep
B	250 ,,	6–8 hours	,,	Patient cannot sleep without the "drug"
C	500 ,,	Nil	,,	No difference in sleep
D	500 ,,	,,	,,	No effect
E	500 ,,	,,	,,	,, ,,
F	500 ,,	,,	,,	Loses a few days off work every month because of night attacks of asthma
G	500 ,,	,,	,,	No difference in sleep
H	500 ,,	,,	,,	No effect
I	750 ,,	,,	,,	,, ,,
J	750 ,,	,,	,,	,, ,,
K	500 ,,	,,	,,	,, ,,
L	500 ,,	,,	,,	Lost 2 weeks off work in the past 4 months because of night attacks of asthma
M	250 ,,	,,	,,	No difference in sleep
N	250 ,,	,,	,,	,, ,, ,, ,,
O	500 ,,	,,	,,	No effect

The rest of the patients did not show any improvement in sleep or reduction of nocturnal attacks of asthma while taking placebo capsules.

Discussion

The ideal treatment of bronchial asthma and its nocturnal attacks would be the removal of the various factors which bring on the attacks. This is not always possible as in a case of intrinsic asthma with strong psychological elements. In patients undergoing desensitization to inhalants and having disturbing nocturnal attacks of asthma, a good hypnotic will contribute greatly to successful treatment. Many asthmatic patients take their troubles to bed with them. A mild but rapid sedation eliminates the worry and anxiety, and a better sleep is possible until morning. In long-standing asthma complicated by chronic bronchitis and emphysema, sedation is very important and a difficult problem. In some old asthmatic patients both chronic bronchitis and ischaemic heart disease contribute to the symptoms of asthma. The choice of a hypnotic may present difficulty. Methylpentynol is very useful in such cases because it does not depress the respiratory centre. Methylpentynol is safe and well tolerated by children. It is dangerous to combine methylpentynol with barbiturates, and a death was recorded recently from such combined administration (*Lancet*, 1954).

The necessity for a control trial is well illustrated by Case B. This patient slept well on a 250-mg. capsule of placebo. It is widely recognized that some asthmatic patients improve on inert tablets or injections. The problem of clinical experiments and their control groups was recently discussed by

Reid (1954). He pointed out that some of the control groups are not properly selected and some of the experiments would be unethical to carry out. This investigation was simple and free from dangers. Although the number of patients was small—only 15 patients in each group—I found out that methylpentynol is a useful adjunct in the management of asthmatic patients.

Summary

Difficulties in choosing the right hypnotic for asthmatic patients are emphasized with special reference to morphine.

A brief description of pharmacological action of methylpentynol is given.

A clinical trial was carried out with methylpentynol on 15 patients suffering from bronchial asthma whose sleep was disturbed by asthmatic attacks. A similar group of 15 patients received a placebo. The results of treatment are presented.

The value of methylpentynol as an adjunct in the management of bronchial asthma is discussed.

My thanks are due to Mr. K. McIver, chief group pharmacist, North Lonsdale Hospital, and his staff for co-operation in this clinical trial; and to Dr. A. P. B. Waind, consultant physician, for his criticism in preparing the paper. British Drug Houses Ltd. supplied the methylpentynol ("somnesin") and blank capsules.

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SICKLING PHENOMENON IN NORTHERN GREECE

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Recent investigations for sickling in Greece showed that the sickle-cell trait is not a rare finding. After the investigation by Makrycostas[1] of the first sickle-cell anaemia cases in people originating from an isolated village of the Sparta district, several cases of sickle-cell anaemia and trait were reported, affecting people from different districts of Greece.[2–15] Choremis *et al.*[10 11] found a focus of sickling in Thebes, close to Athens; the frequency of the sickling phenomenon in this area is not known.

The Investigation

A few cases of sickle-cell anaemia in people originating from the Chalkidiki district of Northern Greece were reported by different writers.[12–15] Several cases of sickle-cell anaemia admitted to our clinic from Chalkidiki gave us the opportunity for a wide and systematic investigation of the sickling phenomenon in Northern Greece, by examination of people of different origin living in this area.

The sodium bisulphite method was used because of its sure and rapid results and its simplicity (read after 30 minutes). We have several times repeated most of our examinations, so that the findings can be looked upon as reliable. We examined mostly schoolchildren aged from 6 to 12 years, because we thought that they best represented a large number of the families of the area under investigation.

A total of 7,063 subjects were examined. Among these were 5,008 indigenous people from families who had lived in the villages for several centuries without mating with strangers, and 2,055 people of varied origin (254 natives speaking a Slav dialect, 208 refugees from Eastern Roumelia, 380 refugees from Eastern Thrace, 578 refugees from the Russo-Turkish border, 180 refugees from the Smyrna area, 163 Turks of Western Thrace, and 292 gipsies). In these 2,055 people the test was definitely negative except for two positive cases whose parents originated from Smyrna (Asia Minor).

A total of 37 villages of indigenous people were covered, in 22 of which some cases of sickling were found. In these 22 villages 3,583 persons were tested and 537 showed the sickling phenomenon. In the remaining 13 villages the investigation gave negative results. The highest incidence of sickling was found in the southern part of Chalkidiki district (Sithonia Peninsula). In the village of Sykia we tested 846 out of the 2,400 inhabitants and found 265 positive (31.3%). In the village of Parthenon the sickling rate was 32%, in St. Nicholas village 24%, in Nikiti 19%, and in Ormylia 18%. The incidence of sickling in the remaining part of Chalkidiki and generally in Northern Greece ranges from 2 to 14%, as is clearly seen on the map printed overleaf.

Incidence of Sickling in N. Greece

No.	Villages	No. Examined	Age in Years	Sickling Positive	%	Origin of People Examined
1	Sykia	846	1–76	265	31·3	Indigenous
2	Parthenon	153	5–12	49	32·0	,,
3	Nikiti	143	5–13	27	19·0	,,
4	St. Nicholas	101	2–12	24	24·0	,,
5	Ormylia	103	5–12	18	18·0	,,
6	Valta	196	1–60	25	12·8	,,
7	Kallithea	90	6–12	8	8·8	,,
8	Pazarakia	150	4–50	21	14·0	,,
9	Furka	92	2–15	2	2·2	,,
10	Kallandra	90	3–20	2	2·2	,,
11	Polychronon	160	4–56	13	8·7	,,
12	Kapsochora	96	6–11	1	1·0	,,
13	Paliouri	160	2–80	16	10·0	,,
14	Kassandrinon	46	6–12	0	—	,,
15	Chanioti	62	5–30	0	—	,,
16	St. Paraskevi	50	6–12	0	—	,,
17	Nea Skioni	40	3–45	0	—	,,
18	Stageira*	—	—	—	—	,,
19	Epanomi	183	7–14	5	2·7	,,
20	St. Prodromos	177	6–12	0	—	,,
21	Zangliveri	172	2–14	0	—	,,
22	Hortiatis	159	5–14	0	—	,,
23	Xylopolis	90	2–60	0	—	,,
24	Halastra	108	7–13	4	4·0	,,
25	Klidi	67	7–14	4	6·0	,,
26	Tsinaforon	151	3–17	14	9·2	,,
27	Korifi	142	4–14	18	12·6	,,
28	Loutros	102	7–18	6	6·0	,,
29	Leptokaria	106	3–14	3	3·0	,,
30	Fytia	150	4–13	0	—	,,
31	Nigrita*	—	—	—	—	,,
32	Aidonochorion	136	8–15	4	3·0	,,
33	Paleokomi	100	5–27	6	6·0	,,
34	Prosotsani	220	6–12	0	—	,,
35	Gratini	86	1–60	0	—	,,
36	Kosmion	76	4–13	0	—	,,
37	Soufli	205	1–50	0	—	,,
		5,008		535		
38	Vrahia	92	7–12	0	—	Slav. dialect
39	Kimina	162	8–14	0	—	,, ,,
40	Trikalla	168	7–14	0	—	Refugees, E. Roumelia
41	Vathylakos	162	7–13	0	—	Refugees, Smyrna
42	Neon Petritsi	238	7–40	0	—	,, mixed
43	Fitoki-Flamburon	181	7–16	0	—	Gipsies, Christian
44	Stavrupolis	108	1–30	2	—	Refugees, mixed
45	Lekani	160	3–45	0	—	,, ,,
46	Kechrocampos	102	7–65	0	—	,, ,,
47	Paranestion	86	2–70	0	—	,, ,,
48	Komotini	143	4–8	0	—	Mixed people
49	Arisvi	82	6–12	0	—	Refugees, E. Thrace
50	Aratos	163	5–58	0	—	Turks, W. Thrace
51	Elafochori	97	2–14	0	—	Refugees, E. Thrace
52	Elafochori	111	3–38	0	—	Gipsies, Moslem
		7,063		537		

* Positive cases noted.

Origin of the Phenomenon

The question now arises, what is the origin of the sickling phenomenon and what is the reason for such a high incidence in Greece? Herrick[16] found in 1910 the first case of sickle-cell anaemia in an American negro. Later, other investigators reported cases exclusively in negroes or in half-castes. This distribution of the phenomenon led different authors to the thought that sickling appeared only in negroes.

On the other hand, Mediterranean anaemia was not found in coloured people during the early days of the investigation.

These two facts led us to regard both diseases as exclusively racial—that is, sickling in negroes and Mediterranean anaemia in whites. But in recent years several indisputable cases of Mediterranean anaemia have been found in coloured people.[17] Four cases were reported in negroes, and the trait was found in a large number of their relatives,[18 19] also a combination of Mediterranean anaemia and C-haemoglobin.[20] On the other hand, 14 cases of Mediterranean anaemia and trait in their relatives were reported in Chinese people[21–29] and 26 cases in Thai people and half-castes.[29] Apart from the above-cited cases, other authors report five cases in Indian children,[30] one in an American Indian child,[31] and cases in Egyptian children.[32–34] We must therefore reconsider the thesis that these morbid conditions affect only one race.

The hypothesis that sickle-cell disease was an exclusive phenomenon of the negroes and the half-castes did not seem well founded, since Cooley and Lee[34] and other authors[1 35–37] reported cases in white people in whom mixture with negroes could be excluded.

Introduction into Greece

Yet this trend of thought was evident in the attempts to explain the sickling phenomenon in the Mediterranean Basin, where, for geographical as well as for historical reasons, the presence of negro blood in the whites of this area was taken for granted. This was thought to be a satisfactory explanation of the sickling phenomenon in Greece, although historical sources (classic, Byzantine,[38] and more recent writers[39 40]) admit no negro invasion of Greece apart from pirate raids executed mainly by Saracens, who are, as is well known, of Arabian origin (Spanish Arabs).

It is worth mentioning here that a recent investigation in Africa has disclosed that the incidence of sickling phenomenon in Arabian tribes is the lowest recorded in that continent (0–2%).[41] Generally, it showed us that the distribution of sickling in Africa is very interesting. The highest rate occurs in Central Africa[41 45–59] and diminishes towards the north[41 50] and the south.[60–65] This distribution is probably related to the way of living of the tribes exposing the gene (static or not) to intermarriage, environmental factors, etc.

The same factors exist probably in Chalkidiki, the area under investigation. This district was from ancient times up until now the theatre of frequent wars, which caused a pronounced reduction in the population and resulted in adverse living conditions and the formation of highly inbred, static groups of population.

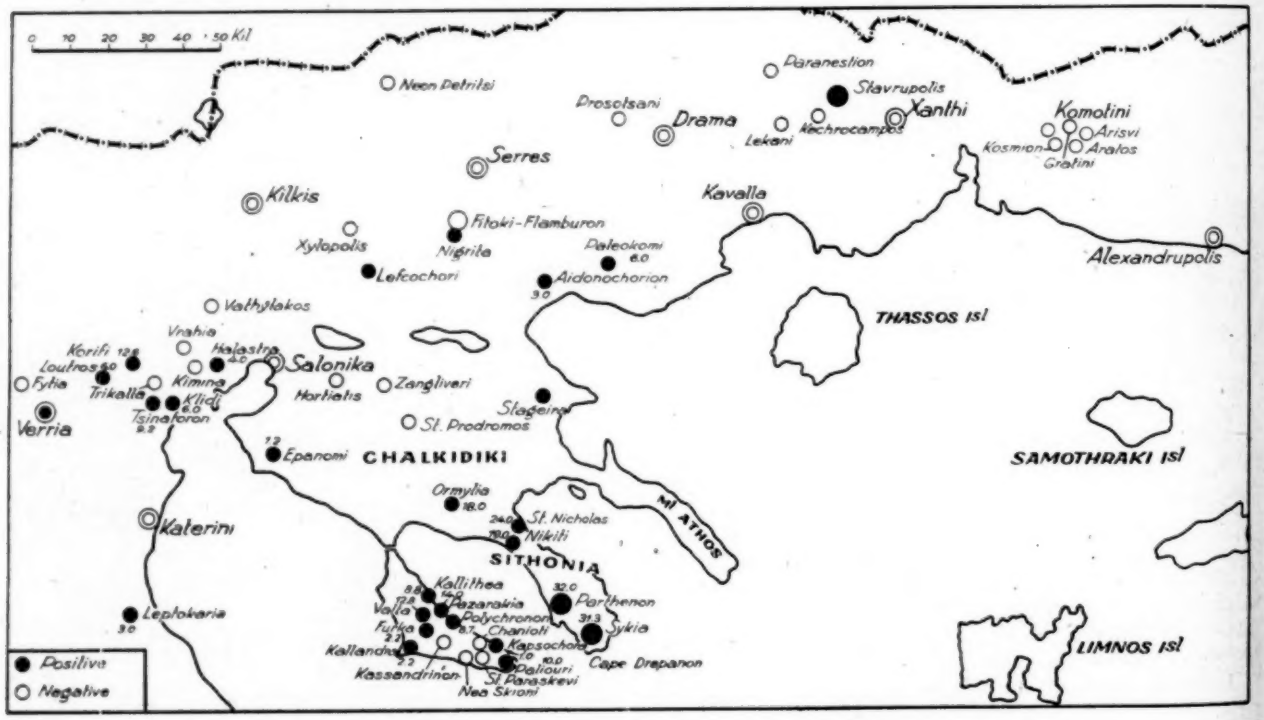
It therefore seems reasonable to conclude that the sickling phenomenon in Greece, which appears in several areas among highly inbred groups, has a common cause—for example, mutation—and is an indigenous, local, and static condition of the inhabitants of those areas. We would mention here that some time ago we also developed a parallel view for the pathogenesis of Mediterranean anaemia.[42–44]

Choremis *et al.*[11] agree with this view of the pathogenesis of sickling phenomenon, stating that sickling in Greece may theoretically be attributed to mutation of the gene and to the influence of malnutrition and malaria and intermarriage among Greeks during the last few centuries.

From recent data at our disposal, however, we cannot agree that malaria is a factor responsible for sickling. These data are included in a paper to follow.

Relation of Malaria to Sickle-cell Trait

Possibly malaria is indirectly responsible for the wide distribution of sickling in some areas of Greece. Knowing the resistance of heterozygotes to malaria, and the fact that the area under consideration was in pre-war times a hyperendemic area, we think that this disease, by eliminating healthy people, increased the frequency of sicklers and so helped the multiplication and perpetuation of the gene. This is a possible means by which malaria was acting to balance out counter-selection.



Map showing distribution of sickling in Northern Greece.

Sickling phenomenon can be regarded as a particular characteristic of any race which shows it in the absence of admixture with another race in which it exists. Its higher incidence around the Mediterranean could be accounted for by the suggestion that some races of the Mediterranean basin, with a few exceptions in other parts of the world, appear to be more prone to develop a mutation affecting their blood-forming tissue. At the same time some unknown geophysical and other factors, one of which may possibly be malaria, favour the high frequency of this mutation in these areas of the globe.

Conclusions

The sickling trait exists in Northern Greece, particularly in Chalkidiki, where in the Sithonia Peninsula the rate is 32%, in the neck of the same peninsula the rate is 18–24%, in the Kassandra Peninsula and in the plain of Salonika it reaches 14%, and at the foot of Pangaion Mountain it is 6%.

The sickling phenomenon is mainly observed among highly inbred groups of natives; it is an indigenous, local, and static condition of this area.

The sickling is due to a mutated gene. Its high frequency and manifestation in a given area can be accounted for by inter-marriage and the elimination of the influence of counter-selection by malaria.

Mediterranean and sickle-cell anaemias must not be regarded as exclusively racial diseases, since many cases have been observed (*a*) of Mediterranean anaemia among coloured people (negroes, Chinese, Thais, Egyptians, Indians, and American Indians), (*b*) of sickle-cell anaemia among white people in whom any admixture with negro blood must definitely be excluded.

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COMPATIBILITY OF SICKLING WITH MALARIA

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The appearance of severe hereditary anaemias in areas where malaria has been endemic for many centuries raises the question of how far malaria can be considered to be connected with the aetiology of these anaemias. We rejected such a connexion for Mediterranean anaemia[1–3] because we had never found malaria in our patients or their relatives. On the other hand, according to some authors the tentative treatment of this disease caused no improvement of the anaemia or any decline in the fever when this was present. Some trials of experimental transmission of malaria from patients suffering from Mediterranean anaemia into animals (*Macacus rhesus*, etc.) were unsuccessful.

Several writers have tried to correlate sickle-cell anaemia and trait with malaria. But recent clinical observations and experimental findings show little compatibility between these two morbid entities. Many workers in Africa, observing the low frequency of malaria in sicklers in contrast to non-sicklers, have concluded that sicklers are more resistant than non-sicklers because they are possibly protected by some unknown factor against attack by malaria parasites. They also think that abnormal red cells are less subject to parasitism than normal cells, and so children bearing the trait and living in malaria-stricken areas have a better chance of reaching adult life than children with normal blood.[4–8]

On the other hand, a different opinion was given by Edington[9] and Moore *et al.*,[10] who found in Africa (Gold Coast and Nairobi) the same incidence of malaria in sicklers as in non-sicklers. It is worth pointing out, however, that Edington counted 500 malarial parasites

per c.mm. in sicklers and 1,000 per c.mm. in non-sicklers. Perhaps these findings, obtained in hyperendemic areas, are due to local conditions—that is, to mass infection, diminution of the resistance of the body for different reasons, etc.

Investigation in Greece

We had an opportunity of investigating this subject in Chalkidiki, where malaria is endemic and the population shows the highest rate of sickling known in Greece.

Making use of lists supplied by the Department of Malaria in Northern Greece, we examined 136 out of 174 cases of malaria confirmed by microscopical examination and reported during the three years (1952–4). These patients came from four villages with the highest rate of sickling known in Greece (32%, 24%, 19%, 18%). The mean rate of sickling in persons suffering from malaria in this area was only 5.8%. On the other hand, the mean sickling rate in 500 unselected individuals examined in this area was 23.6%. It is noteworthy that the number of sicklers with malaria is extremely low, whereas one would expect it to be similar to that of non-sicklers, because the existing conditions of infection and sensitiveness are the same (Table I).

TABLE I.—*Percentage of Sickling and Malaria in Examined Cases*

Villages	Unselected Sickling			Malaria		
	No. Exam.	Positive	%	No. Exam.	Sickling Positive	%
Parthenon ..	153	49	32	28	1	3·6
St. Nicholas ..	101	24	24	40	2	5·0
Nikiti	143	27	19	31	3	9·6
Ormylia	103	18	18	37	2	5·4
Total ..	500	118	23·6	136	8	5·8

Blood investigations for sickling were made on siblings of families affected by malaria. This was done in order to secure, so far as possible, the same conditions of living and sensitivity to malaria infection. Only the siblings of the children infected by malaria were examined. It seemed to us that the results could give us a better picture of the relationship between malaria and sickling as well as the frequency of the former in persons with or without the latter condition. In fact, we noted that, in the families of sicklers, the members who were not infected by malaria parasites were mostly positive for sickling, whereas those who were negative for sickling were infected more often by malaria (Table II).

TABLE II.—*Families with Positive Sickling and Malaria*

Name	Age (Yrs.)	Malaria	Sickling	Name	Age (Yrs.)	Malaria	Sickling
St. Nicholas				Parthenon			
K. N. S.	9	+	−	E. Th. K.	7	+	−
V. N. S.	7	−	+	D. Th. K.	1	−	Micro-cyt.
A. N. S.	6	−	+				
H. N. S.	10	−	+	M. Th. K.	12	−	−
M. N. S.	3	−	+	A. Th. K.	5	−	−
S. N. S.	30	−	+	T. Th. K.	38	−	+
A. D. P.	15	+	−	A. N. P.	29	+	−
A. D. P.	4	−	+	E. N. P.	2	+	−
G. D. P.	8	−	+	E. N. P.	6	−	+
				N. E. P.	35	−	+
D. A. S.	7	+	−				
M. A. S.	10	−	+	B. I. E.	9	+	−
				I. I. E.	7	−	+
A. Th. D.	11	+	−				
D. Th. D.	8	−	+	A. D. H.	18	+	−
				A. D. H.	8	−	+
A. Th. S.	6	+	−				
G. Th. S.	1	−	+	B. K. K.	8	+	−
				T. K. K.	4	−	+
				N. K. K.	7	−	−
Ormylia				Nikiti			
I. H. M.	12	+	−	G. I. M.	14	+	−
M. H. M.	38	+	−	A. I. M.	11	−	+
A. H. M.	11	−	−	N. I. M.	8	−	−
G. H. M.	7	−	−				
H. I. M.	46	−	+	G. A. K.	8	+	−
				N. A. K.	7	−	−
G. H. E.	8	+	+	M. A. K.	13	−	+
A. H. E.	10	−	−				
L. H. E.	5	−	+	K. M. A.	19	+	−
H. I. E.	47	−	+	G. M. A.	7	−	+

We must admit, with Allison,[4] Brain,[5] and Mackey and Vivarelli[8] that the coexistence of malaria and sickling is of a low order. Sicklers show a stronger resistance against the infection. Their red cells are less susceptible to malarial parasitism, and this may be due to unsuitable environment because of the presence of the abnormal S-haemoglobin.

We also observed that in sicklers infected by malaria the test for sickling, using the sodium bisulphite method, was not always complete for all their red blood cells, in contrast to the cases in which only the sickle-cell trait was present.

Paper electrophoresis revealed an abnormal haemoglobin following the normal haemoglobin, like the haemoglobin of the trait.[11] Unfortunately it is not possible to separate the abnormal haemoglobin quantitatively by paper electrophoresis.

The infestation of some red cells with parasites in the case of sicklers could be explained by the possibly smaller amount of S-haemoglobin present in these cells, unless some special condition of the stroma favours the entrance of the parasite.

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PENICILLIN ANAPHYLACTOID SHOCK

BY

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The clinical advent of penicillin in 1943 opened the antibiotic era. Within a decade, however, the threat of anaphylactoid reactions from this drug gradually emerged[1–23] and is now a grave concern.[24–59] Indeed, penicillin is the prime cause of drug-induced anaphylactoid reactions. It is convenient here to refer to anaphylactoid rather than anaphylactic shock, bearing in mind that some of the reported cases are hardly true examples of the latter.

Casuistic reports continue to appear, and the cautionary remark of Gilman,[60] "... One must conclude the guilt of usage rather than of the substance," merits consideration. Smith and Walker[61] emphasized that the ability of penicillin "to sensitize and to cause serious and even fatal accidents should not be minimized." The continued extensive use of this valuable drug means that many patients are becoming sensitized to an anaphylactic degree. Under these circumstances the precept of Hippocrates, "Primum non nocere," is apt.

This review, while not intended as a detailed analysis of universal literature, provides a practical discussion of the extent of the problem and of suitable prophylaxis. This subject is not the sole concern of the pharmacologist or allergist, as there must be few doctors, irrespective of specialty, who are not frequent prescribers of this drug. Hence it may fall within the purview of

any doctor to recognize and treat this emergency. Severe anaphylactoid reactions to penicillin have been fairly adequately described but inadequately discussed. The accompanying illustrative case report is sufficiently instructive to record.

Case Report

On March 4, 1953, a robust Army officer aged 47 walked into the casualty department of Whipps Cross Hospital at 9.30 p.m. for treatment of a cellulitis of the right leg. The duty house-physician ordered one mega unit of crystalline penicillin intramuscularly and a kaolin poultice locally. At 10.15 p.m. a staff-nurse gave the injection into the patient's right arm. Although the vague possibility of accidental venepuncture exists, there was no reason to suspect this.

Ten minutes after the injection, which had caused no discomfort, the patient calmly stated, "Penicillin made me feel dreadful the last time I had it." At precisely 10.30 p.m. the patient, now seated in the treatment room, began to groan. The staff-nurse rushed to investigate. She found the patient still seated, but with bulbar conjunctival congestion and a heliotrope facies. The nurse immediately called out for assistance. The patient's respirations had now ceased, and apnoea lasting two minutes ensued. However, spontaneous respiration resumed without resort to artificial respiration or analeptics. During the apnoea the patient became pulseless, with widely dilated pupils, profuse perspiration, cold and clammy extremities, and urinary incontinence. No epileptiform movements were observed. He had now been placed supine on a mattress, where he lay unconscious for the next fifteen minutes. The only immediate treatment given was forward traction of the tongue, the application of warmth—his temperature was then 97° F. (36.1° C.)—and continuous oxygen administration.

At 10.45 p.m. he was first seen by one of us (R. J. C.). Moderate shock persisted, but there was now no respiratory embarrassment. He lay still with mild cyanosis, pin-point pupils, an impalpable pulse, and a low blood pressure (60/40 mm. Hg). No other abnormal signs were elicited. Consciousness was now returning sufficiently for him to mutter a few words. He complained only of transient epigastric pain. Mercifully, recovery now seemed assured, and in the hope of hastening this he was given 3 ml. (0.75 g.) of nikethamide intramuscularly, as there were no accessible veins for more direct administration. He was then transported to the ward, where a heat-cage was fitted over his bed. Two hours later his temperature had risen to 100.4° F. (38° C.), his blood pressure to 100/70 mm. Hg, and he stated that he was perfectly well. An electrocardiogram taken immediately on his arrival in the ward showed sinus tachycardia (120 a minute) and a reduced amplitude as the only abnormalities. With bed rest and a course of chlortetracycline ("aureomycin") his cellulitis cleared within a week.

His history was non-contributory apart from recent events, which were highly significant. He had a mild attack of nephritis in 1918, pleurisy in 1926, and infective hepatitis in 1945, and had since remained fit until about two weeks before the present admission.

One evening at that time, while visiting friends, he complained of a sore throat, for which one of them gave him two penicillin lozenges. He immediately sucked one of these lozenges, but became alarmed five minutes later by "a tingling sensation creeping up his neck and an almost simultaneous burning feeling as if his face was on fire." Within a few minutes he felt "as if he was being gently but surely choked." He then dashed outside for fresh air, but promptly decided to return hastily to his residence, some 400 yards away. After walking about 100 yards in a dazed state a peculiar visual upset appeared. He could see "about ten of everything coming towards him." On arrival at his door he was "unable to identify the correct one out of some apparent ten doors" in front of him. His left shoulder struck something solid and he gyrated and was pitched to the ground. He could only vaguely recall being assisted inside, laid on a settee, and covered with blankets. His teeth now began to chatter uncontrollably, and he fell into a deep sleep. One hour later he awoke suddenly on the arrival of his doctor, and he stated that he felt quite well again. He was then informed by his doctor that he must have been allergic to penicillin. The patient had since maintained the pious hope that he would be less allergic to penicillin.

Later exhaustive inquiry revealed no other history of allergic disease, no syncope, epilepsy, or earlier administration of penicillin. There had been no known epidermophytosis. Neither subsequent skin-testing nor desensitization to penicillin was seriously considered in view of these clear-cut hyperallergic reactions to this drug. Instead, he was instructed to carry a card under the "cellophane"-covered compartment of his wallet, indicating boldly that he reacted violently to penicillin.

Discussion

Although the fact that many clinicians and practitioners have not encountered this catastrophe is evidence of its rarity, relevant comprehensive publications refute this view. A few selected illustrations will suffice. Bateman *et al.*[22] referred to three anaphylactoid reactions with two fatalities from this drug. Siegal *et al.*[25] also reported three such reactions with one death. Mayer *et al.*[26] added six cases, including one fatality. They described a near-fatality from an intradermal test with only 10 units of penicillin G. Curphey[30] reported two more fatalities. Both Feinberg *et al.*[31] and Sterling[35] recorded a series of nine cases. Five of those recorded by Feinberg *et al.* died. During a panel discussion[39] on this subject nine more cases were cited. Welch *et al.*[41] provided the first systematic study of this phenomenon. Briefly, their survey of the records of 95 hospitals totalling 51,000 beds disclosed 59 anaphylactoid reactions from penicillin with 19 deaths. It is noteworthy that one of these fatalities followed the ingestion of one tablet of dibenzylethylenediamine dipenicillin G (either 100,000 or 200,000 units). They also referred to a report[23] of 25 further severe reactions, involving five fatalities, from the use of penethamate hydriodide ("neo-penil"; "estopen") submitted voluntarily by the manufacturers, Smith, Kline, and French. Indeed, this firm (personal communication) discerningly discontinued the supply of this drug early in 1954. More recently Rosenthal[53] described no fewer than eight fatal penicillin reactions, while Swift[58] added ten cases with one death. This expanding subject was reviewed earlier by Kern and Wimberley,[44] and more recently by Garat and Landa.[52] Certain details of the earlier literature, mentioned by them, have been conveniently omitted here.

Examination of the events in our patient provides grounds for a reassertion of the following points.

(1) Oral medication with penicillin is not devoid of risk. This contention, however, does not invalidate the view of Kern and Wimberley[44] that this route provides a greater measure of safety than the parenteral routes. Nevertheless, our patient sustained a moderate constitutional reaction five minutes after sucking a penicillin lozenge containing only 1,000 units of penicillin. This, our patient averred, was his first administration of this drug. One hesitates to predict the outcome if he had ventured to suck the second lozenge. The reaction described is, however, not unique, for Madalin[50] reported a similar but more profound response. His patient had cacogeusia within two minutes of commencing to suck a lozenge containing 20,000 units of crystalline penicillin. The lozenge was promptly expectorated, and the actual anaphylactoid dose was gauged as being less than 2,000 units. His patient had previously had penicillin, to which he was later shown to be extremely sensitive.

(2) A negative history of penicillin administration is not foolproof against a moderately severe reaction, as evidenced by our patient's response to the penicillin lozenge. Contrary to the experience of Mayer *et al.*,[26] severe anaphylactoid reactions have occurred in patients who had no

knowledge of previous penicillin medication.[53 54] Admittedly, an absence of previous contact with this drug does not harmonize with the theoretical concept of true anaphylaxis.

In these patients, Cormia *et al.*[1] considered, there was usually a history of epidermophytosis linked with their sensitization to penicillin. A further simple explanation is that there are many modes of administration of penicillin—for example, eye, ear, and nasal drops; inhalations; medicated tulle gras; intrapleural and intrathecal instillation, etc. A patient may have received the drug under these circumstances and yet be unaware of this fact in a subsequent interrogation. It is apt to note here that even the topical application of this drug[11 49 55 56] may provoke an anaphylactic response. In Ruskin's patient[55] the route was percutaneous, while in the case described by Carter and Cope[56] an oculentum was responsible.

Moreover, although penicillin has been given without previous adverse reaction, this fact constitutes no guarantee against an anaphylactoid reaction.[54] Frank danger lies in resuming penicillin treatment and not during a course of injections.[21 44] It is essential to be alert to this group because of the apparent safety implied by the history.

(3) It seems improbable in our patient that a fortuitous intravenous escape of part of the intramuscularly administered penicillin was responsible for the major reaction. Surely, the time-lag of fifteen minutes from the injection to the dramatic onset of the event offsets this possibility. Moreover, whereas a lozenge with only 1,000 units of penicillin produced a moderate constitutional reaction in five minutes, he remained symptomless for at least ten minutes after the intramuscular injection of 1,000,000 units.

Instantaneous severe reactions from intramuscular injections of penicillin have often been recorded. One explanation advanced is that the accidental intravenous penetration or permeation of the drug could accentuate or even cause these reactions. Bell *et al.*[39] discussed this possibility, which may apply to some patients in whom there is evidence neither of previous sensitization nor of subsequent incident in relation to a severe reaction to this drug.

Occasional reports mention cacogeusia as an early symptom of a severe reaction to penicillin. Whereas Waldbott[5] regarded this symptom as indicative of a direct intravenous mishap, there is evidence against this assertion. For instance, this symptom can be a feature in the similar misadventures from the oral[50] and percutaneous[55] and ocular[56] routes, unrelated to acupuncture.

Lack of space precludes a description of the assorted patterns of severe penicillin reactions. It is, however, worth recalling that Batchelor *et al.*[62] reported a bizarre immediate reaction to intramuscular injections of procaine penicillin. Six of their eight patients experienced angor animi without any sign of syncope. It is also impossible to discuss here the modes and risks of testing for sensitization* and of desensitization, the severe delayed "serum-sickness-like" reaction, and the hazards of intrathecal administration of penicillin.

Instead, it will be more rewarding to summarize a schematic approach designed to minimize the incidence and degree of these anaphylactoid shocks. For this purpose a cumulative review is presented below. Only certain broad principles with a keynote of caution can be suggested. As Boger *et al.*[33] remarked, "there are no infallible rules covering the phenomena of hypersensitivity to penicillin."

Suggested Prophylaxis

(1) *Reduction of Increased Sensitization.*—The elimination of the indiscriminate use of penicillin, regardless of route or preparation, will minimize a needless increased sensitization of the population. The extreme price of using penicillin when it is not indicated was manifest in a report[53] of eight such anaphylactoid deaths, two of which followed the use of this drug for the treatment of the common cold.

(2) *Precise Anamnesis.*—Routine interrogation concerning previous penicillin therapy with particular attention to reactions (an unfortunate oversight prior to our patient's intramuscular injection) will reveal the need for caution. This inquiry should include pruritus, as pointed out by Swift,[54] since among ten of his patients showing anaphylactoid reactions eight were aware of this symptom following a previous injection of penicillin. A similar inquiry concerning an allergic diathesis is expedient, since many of the reported major reactions have been in asthmatic subjects.

(3) *Decision in Doubtful Cases.*—Where penicillin is specifically indicated but could reasonably be expected to be hazardous, the decision clearly lies between the selection of one of the many other antibiotics (chlortetracycline, oxytetracycline, tetracycline, erythromycin, etc.), and extremely cautious and thorough testing for hypersensitization[26 31 39 44 58] if penicillin is still preferred and time avails. As alternatives, the concurrent administration of antihistamines and the substitution of penicillin O require further investigation before a dogmatic answer on their value is possible. Their value may well be limited to dermal sensitization reactions to penicillin G, as their use otherwise might engender a false sense of security. There is no persuasive evidence that one particular penicillin preparation is safer than another or that oral therapy is very much safer than systemic. The use of greatly retarded repository penicillin products is a potential hazard to be evaluated.

(4) *Cautious Technique of Injection.*—The injection technique should include: (*a*) Use of a fine-bore needle for crystalline penicillin solutions; but, conversely, a wide-bore needle for procaine penicillin suspensions to obviate its occlusion by the crystals. (*b*) Routine preliminary aspiration for blood while the needle is *in situ* for a subcutaneous or intramuscular injection of the drug. Alternatively, the procedure cited by Bell *et al.*[39] appears commendable. Here a separate insertion of the needle and a careful watch that no blood escapes precede the attachment of the loaded syringe. (*c*) Waldbott's recommendation[5c] of a preliminary injection of one or two drops of the penicillin preparation, followed by a safety pause of 45 seconds before delivering the main injection. This is of course equivalent to a test dose. (*d*) Choice of the subcutaneous rather than the intramuscular route in doubtful cases. (*e*) The selection of the upper arm as the site of injection so that in emergency a tourniquet can be readily applied.

There is no commercially available preparation of an anti-hyaluronidase type nor a penicillin neutralizer such as penicillinase for dire emergency.

(5) *Exemplary Surveillance and Preparedness.*—This includes a willingness of both the administrator and the patient to remain at hand for twenty minutes after the injection, thus providing a relatively safe period of vigilance for the severe immediate anaphylactoid reactions. Conversely, Kern and Wimberley[44] stressed the rapidity of onset of symptoms in some of the reported cases in which fatality supervened before any full-scale attempt at resuscitation could be instituted. In many other cases, however, there has been a longer latent period of five to ten minutes. The supervisor should be alert for the warning sign of congestion of the bulbar conjunctivae[54] and for the first complaint of tingling, difficulty in breathing, giddiness, or faintness indicative of impending anaphylactoid shock. It is suggested that, where possible, a "penicillin-resuscitation tray" be immediately available and stocked with liquor adrenalinae, and ampoules for the intravenous use of an antihistamine, a vasopressor amine, nikethamide, and aminophylline. As Hoagland[63] has pointed out, the first essential is preparedness to meet the emergency.

(6) *Adequate Documentation and Publicity.*—Cards boldly indicating hypersensitization to penicillin should be retained in the wallet or handbag by the patients concerned. Alternatively, a small disk conveying the same information could be attached from the neck and concealed under the clothing in case the patient should be brought in an unconscious

*A term preferred to sensitivity, which is best reserved for the bacteriological aspects of antibiotic activity.

state for treatment, which might include penicillin. Above all, patients who have been given penicillin in any form should, for their own safety, be told even though no adverse reaction ensued. Swift[58] has shown the value of careful documentation in a clinic where penicillin is widely used.

For the benefit of all concerned, publicity from manufacturers could be increased by the adoption of "manufacturers' slips of caution"[58] displayed on the bottles or included in the packages of all penicillin preparations. Further publication of case reports and/or their submission to a central agency collating such data would permit a true assessment of the frequency of these reactions. Since most injections of penicillin are given by nurses they should be informed that these anaphylactoid reactions require prompt recognition and treatment. As an additional safeguard they should re-question the patients about previous courses or applications of penicillin and ascertain if any apparently related adverse effects had occurred. Here needless confusion is avoided by speaking the simple language of the patient and inquiring if anything went wrong previously rather than using the terms "sensitivity" or "allergic reactions."

Summary

The literature on anaphylactoid reactions from penicillin is briefly reviewed. A further case is reported to emphasize that moderately severe reactions can follow the use of penicillin lozenges and that there are occasional instances of severe reactions even when no history of previous administration of the drug can be elicited. A detailed description of a subsequent profound anaphylactoid shock in this patient is presented. A scheme for reducing the frequency and degree of these catastrophes is outlined.

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Medical Memorandum

Reactions to Intramuscular Iron

A new iron-dextran complex ("imferon") has recently been described (Baird and Podmore, 1954; Cappell *et al.*, 1954; Scott and Govan, 1954). It is reputed to be less toxic and more stable than saccharated iron oxide ("ferrivenin"). The dosage administered is 2 to 5 ml. (100 to 250 mg. of iron) as compared with the usual maximum dose of 5 ml. (100 mg. of iron) of intravenous saccharated iron oxide. Adequate serum concentrations have been obtained after the administration of the iron-dextran complex, the maximum absorption occurring in the first one to two days and the serum iron level falling to normal about the seventh day. Toxic reactions were not observed, but discomfort at the site of injection lasting up to twelve hours and staining of the skin were noted.

Dempster *et al.* (1954) obtained satisfactory results, but encountered local reactions in several patients and had to stop treatment in 2 of their 16 patients. Callender and Smith (1954) encountered four severe reactions in a limited period; two of these occurred soon after injection and two showed a delayed reaction of an allergic character. They gave the patients iron and dextran separately without producing any reaction, and suggest that the combination of iron and dextran may result in a sensitizing compound. Jennison and Ellis (1954) state that all their patients attained a satisfactory haemoglobin concentration. They report a few cases of local reaction; but mild general reactions, including nausea, vomiting, depression, fainting, and skin rash, occurred in 20% of their patients. Ross (1955) reports a delayed allergic reaction in a man of 55 and an early reaction after 1.5 ml. given intravenously to a youth of 17.

Reactions due to intravenous saccharated iron oxide fall into two main groups, early and late. The early consist mainly of cardiovascular collapse and of pain in the chest, back, and limbs possibly due to ischaemia. These occur even after doses of 100 mg. or less. The late (delayed) reactions are uncommon and occur after larger doses, usually 300 mg. or more. Nissim (1954) found only 13 cases of late reaction in the literature, of which only two had suffered an early reaction.

Librach (1953) considers allergy to be an important factor, especially in the production of early reactions, and believes they may be due to a natural hypersensitivity.

It seems as though the new iron-dextran complex may present us with combined early and late (delayed) reactions, the main symptoms of which have been observed previously. The accent is, however, upon symptoms hitherto uncommon. This is to be expected, as the mechanism of toxicity varies with the other properties of the whole molecule injected (Nissim, 1954).

CASE REPORT

On September 22, 1954, a married woman aged 46 was admitted to hospital for total hysterectomy. She had suffered from menorrhagia for two years, and on examination the uterus was enlarged by fibroids to the size of a

16-weeks pregnancy. On the 24th total hysterectomy was performed by Mr. Dickinson. There was very little loss of blood and the patient's condition was satisfactory.

The immediate post-operative course was uneventful. The haemoglobin, which was 62% on admission, had fallen to 58% on the 27th. Intravenous iron therapy was begun the next day. Saccharated iron oxide ("ferrivenin") was given daily up to a total of 34 ml. (≡ 680 mg. of iron) in eight days, the last dose, 5 ml. (≡100 mg. of iron), being given on October 6.

At 2.30 p.m. on October 7, 2 ml. of iron-dextran complex was given intramuscularly into the left buttock. The injection was slightly painful, but the patient did not complain at the time. Ten minutes after the injection she had a feeling of tightness in the chest and nausea. At 3 p.m. she felt faint and giddy, and also complained of a pricking sensation in the palms of her hands which she likened to severe "pins and needles." She felt cold, began to shiver, and was given an extra blanket and a hot-water bottle; she then slept from 3.30 to 5 p.m. On waking she had a mild generalized headache. Her temperature was 99.6° F. (37.6° C.), and her pulse, which had not risen during the rigor, remained between 80 and 90. The B.P. was 120/70.

At 6.30 p.m. she vomited 10 oz. (280 ml.) of altered food, after which the headache was more severe and mostly frontal. She complained of swelling of the eyelids and said that she felt "quite ill," but was pleased that the tight feeling in her chest had gone. Her eyes showed only slight swelling of the upper lids.

At 9 p.m. the headache, which was much worse, was frontal and occipital, with most of the increasing pain at the back. She complained of pricking in both eyes and required considerable persuasion before she would open them, as that made the pricking sensation much worse. The eyes were watering profusely, the lids were swollen, and a mild conjunctivitis was present. Sight was unimpaired. Chlorcyclizine hydrochloride, 100 mg., was given orally every four hours.

She spent a restless night, being awakened by the pricking sensation in her eyes. Next morning she had a mild frontal headache, which was relieved by aspirin, 10 gr. (0.65 g.). The pricking sensation in the hands and the faintness and giddiness had gone. The pulse remained at 70–80, the B.P. was 130/80, and the temperature was normal.

There was no photophobia, but the pain in the eyes became much more unpleasant when the eyes were opened. She had developed diplopia, and blurring of vision prevented her from reading newspaper headlines. There were no other symptoms. The eyelids were more swollen, the conjunctivitis more marked, and the watering more profuse.

On October 9 there was tingling in the eyes only, but the pricking returned when they were opened. The diplopia improved throughout the day, and had gone by 6 p.m.; the blurred vision also improved enough to allow her to read newsprint. The eyelids remained very oedematous, but the conjunctivitis and excess lacrimation were just as severe.

Next day the eyes were greatly improved and watered only slightly. There was no diplopia and only slight blurring of vision. On the 11th the sight was normal, but there was some tingling at the inner canthus of both eyes. Only very slight conjunctivitis remained. The next day the eyes appeared normal, but the patient complained of tingling and slight blurring of vision after reading for 20 minutes. On October 13 the eyes were normal and the patient was discharged.

At no time did the patient have a rash. The optic disks and fundus oculi were normal throughout. She had never previously shown any allergic manifestations. Adrenaline would probably have controlled the reaction, but was not given, as the patient had developed a marked dislike of injections and we wished to study the course of the reaction under treatment of an oral antihistamine. Two months later an intradermal injection of iron-free dextran and an injection of ferrivenin were given without any ill effect.

COMMENT

Local reactions of pain, tenderness, and staining are fairly common, as is some small rise of temperature and headache a few hours after injection (Jennison and Ellis, 1954). General reactions, both early and late, seem to occur, and, whilst the early reactions are not usually severe, several cases of fainting have been reported. If the allergic theory is correct, these reactions should be controlled by adrenaline, and there is some evidence to support this view (Callender and Smith, 1954).

It is the late reactions, however, that give rise to concern, because many of the patients have returned home before the symptoms develop. These delayed reactions, most of which occur from two to twelve hours after injection, are mostly allergic in nature and can be quite severe or even dangerous. Adrenaline may control these symptoms, but, as one would expect, antihistamines have little or no effect.

It has been found that 40 to 50 mg. of iron-dextran complex intramuscularly raises the haemoglobin level by 1% (Jennison and Ellis, 1954; Baird and Podmore, 1954; Scott and Govan, 1954) as compared with 25 mg. of intravenous saccharated iron oxide; the lower utilization ratio of iron-dextran complex offsets to a great extent the advantage of injecting a larger amount of elemental iron. Furthermore, the maximum response from intramuscular iron-dextran complex occurs in from four to nine weeks, compared with three to five weeks after saccharated iron oxide given intravenously.

The *British Medical Journal* (1954) and Ross (1955) are correct in asking that this iron-dextran preparation should be given a much more extensive trial before its general use is advocated, and meanwhile it should be given to out-patients only after very careful consideration. It should not be used in the routine treatment of anaemia in pregnant women until further trials have been completed.

I wish to thank Mr. J. R. Dickinson for permission to publish this case.

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About 20% of men reaching their late fifties in a reasonable state of working efficiency are compelled by their age or its infirmities to seek lighter work, and a further 10% are incapacitated for all but the easiest tasks, states *New Jobs for Old Workers*, a Nuffield Foundation report by F. Le Gros Clark and Agnes C. Dunne. Study of the 1951 census returns showed 16 occupations in which the proportion of older men is unusually high, and where, out of the total body of men, 37.7% are 55 and over. 71% of watchmen are in this age group—before 1951 some 20,000 older people moved to this job—61.1% of office cleaners, 43.7% of lift attendants, and 37.4% of gardeners. Some work, such as caretaking, seems to have a somewhat restricted field of recruitment, attracting chiefly ex-Army or police pensioners. Of the 16 occupations, only a few seem likely to increase their intake of older people. Progressive mechanization means men can replace women as office cleaners; and more local authorities are using older gardeners to mow lawns and cut hedges; while the occupation of lift attendant has now been reserved for the disabled. The factories and transport provide manpower for alternative jobs; mining, agriculture, and the docks can provide light or part-time work for their ageing employees.

Reviews

AFRICAN DEVELOPMENT

The Development of Tropical and Sub-tropical Countries: with Particular Reference to Africa. Edited by A. Leslie Banks, M.A., M.S., F.R.C.P., D.P.H. (Pp. 217+xvi; illustrated. 18s.) London: Edward Arnold Ltd. 1954.

This book should be read and carefully considered by all concerned with tropical Africa, be they doctors, teachers, Civil Servants, industrialists, or politicians. It is a record of the proceedings of an informal seminar held at Cambridge in 1953 on the development of tropical and sub-tropical countries with particular reference to Africa, and in its pages are reflected the wisdom of 32 distinguished contributors.

Change there is inevitable, for, as Dr. J. A. Logan pointed out, "Because of world-wide economic and social forces, Africa is caught up in the relentless wheel of 'progress.'" This change must therefore be faced and channelled into acceptable directions. By Western standards Africa is underdeveloped, but desirable development in any one direction may have far-reaching and possibly undesirable effects in other directions. Perhaps the greatest value of the seminar lay in helping to limit such undesirable change by bringing together views and experiences of experts in different fields and facilitating integration and discussion of the broad principles of further development. The seminar was fortunate in having Dr. K. A. Busia, of the Department of Sociology, University College of the Gold Coast, to describe from the African viewpoint some of the problems inherent in development. He stressed differences in the way Africans, as compared with Europeans, interpret life. Thus "when an African gets an additional sum of money it is not invested as an economist might advise . . . he probably spends it in having a big funeral for a relation who died three, four, or five years ago. Or he may spend it, when he is living in an overcrowded room and is starving himself and his family, in order that he may get five, six, or seven extra changes of clothing, because prestige is measured in those terms." Appreciation of such points is important if false conclusions are to be avoided. Thus malnutrition in Africans is not necessarily an expression of poverty.

From consideration of such matters the seminar proceeded to study technological development, power and water, food and its production, health, welfare, education, and possible future lines of action. A comprehensive programme, and each discussion embodied the results of much thought and experience. Many of the points made are controversial, but all merit careful consideration. The book cannot fail not only to have an important impact on future development in Africa but also to stimulate and provoke discussion among all who read it.

A. W. WOODRUFF.

BIOLOGY OF BILE PIGMENTS

Biology of Bile Pigments. By Torben K. With, M.D. (Pp. 523+xiii. Danish Kroner 50.) Copenhagen: Arne Frost-Hansen. 1954.

Dr. With's original contributions concerning the bile pigments in health and disease are well known and have established him as one of the authorities on this subject. In the work under review he has collected in monograph form an immense amount of information on the biology of bile pigments and has discussed it as only an expert is competent to do. He has also put forward a number of new ideas, indicated lines for further research, and suggested changes in the presently accepted classification of types of jaundice.

The monograph consists of nearly 400 mimeographed pages (single-sided) of text, well subdivided into chapters and sections, a comprehensive subject index, and an author index. There is also a citation of over 2,000 references, including the titles of the original works; this alone should serve to put every investigator interested in bile pigments greatly into Dr. With's debt, since his survey covers the world literature from before 1800 to the present day. The style of production of the volume inevitably makes it somewhat difficult to handle, and the closely typed pages are not so easily read as is print; nevertheless the reproduction is generally good and the author has aided his readers by carefully used underlining. The monograph bears the date 1954 and has, we are told, taken eight years to write. Most recent work is referred to in addenda or, in the case of Cole and Lathe's work on reversed phase chromatography of bile pigments, by the insertion of a loose page into the text at the appropriate place. There are many typing errors, but the English is good and the whole work is very readable. A welcome feature for those who have not time to read from cover to cover will be the short summaries at the end of every important section.

This is essentially a book for the specialist on bile pigments, and for him it is indispensable. Readers whose work is of a more general character, whether physicians, physiologists, or chemical pathologists, but to whom a knowledge of modern ideas concerning bile pigments and their formation is important, would also do well to study Dr. With's monograph, for it can confidently be prophesied they will find much there of value to them. The peculiar scarcity of tables sometimes makes for heavy reading, but the diagrams and figures are generally clear and adequate for their purpose.

C. RIMINGTON.

POLYPEPTIDES

Polypeptides which Stimulate Plain Muscle. Edited by J. H. Gaddum, F.R.S., Sc.D., M.R.C.S., L.R.C.P. (Pp. 140+vii. 15s.) Edinburgh and London: E. and S. Livingstone Ltd. 1955.

This book deals mainly with polypeptides which are present in the tissues and fluids of the body and which are pharmacologically active. The most notable substances are vasopressin and oxytocin, the two hormones of the posterior lobe of the pituitary body. The others are as yet scarcely known except to the few who study them. A very active one is kallikrein, which is present in saliva, in pancreatic juice, and in urine. In spite of the facts that this has a comparatively high molecular weight and has not yet been isolated in pure form, the intravenous injection into a dog of as little as 0.2 μg. of a concentrated preparation from urine causes a fall in blood pressure. Such an observation suggests that the pure substance must be extremely active and therefore must have an important role in the body. Among the other substances are bradykinin, substance P, darmstoff, angiotonin, cholecystokinin, and the hepato-renal factors V.E.M. and V.D.M. The properties of several of these are similar: they depress the blood pressure and stimulate smooth muscle. Those of the polypeptides which raise the blood pressure—namely, angiotonin and pepsitensin—may be responsible for some forms of high blood pressure. The importance of the others is uncertain, but the instinct to investigate the composition and properties of an active substance present in the body is sound. While such work may seem academic and even uninteresting, it is clear that it may lead to the solution of major physiological and pathological problems.

In the account of these substances in this book there are very few high lights. In a concluding chapter the editor says that the "opinions expressed by the fifteen authors . . . are their own. Their opinions of one another are not always entirely favourable, and it would not be easy to get general agreement about the exact status of all the substances discussed."

J. H. BURN.

ADVANCES IN THYROID STUDIES

Transactions of the American Goiter Association, 1954. Annual Session. (Pp. 483+xii; illustrated. £5.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1955.

To one reader who heard these papers delivered and discussed, formally in the lecture hall and informally in the pleasant purlieus of the Somerset Hotel in Boston, the

newest volume of the *Transactions of the American Goiter Association* recalls so many pleasant memories that an aura invisible to the ordinary reader surrounds even such matters as the inaccuracies involved in the salting-out technique in estimating hydrolysis, or the limitations imposed by the rate of hydration of CO_2 to yield $H+$ and HCO_3- on the transcellular ionic exchanges. But even those less fortunate readers whose memory cannot recall the benign expressions of the pundits, viewed through the special light-filtration effects of an "old-fashioned" or a mint julep, must realize that in this volume are gathered a fairly high proportion of the more significant advances in the study of the thyroid gland which have occurred in the last year in the U.S.A., Canada, and Britain.

Though much of the volume will be found a little too strong for clinicians, a new arrangement reduces many even of the most abstruse papers to sea-level. The biochemical papers have been transcribed into practical terms by such well-known amphibians as Rulon Rawson, and thus the ordinary doctor is able to appreciate without too much strain the ways in which the scientists are contributing to the everyday business of the diagnosis and treatment of thyroid disorders.

RAYMOND GREENE.

THE STORY OF MEDICINE

The Story of Medicine. By Kenneth Walker, M.A., M.B., F.R.C.S. (Pp. 343; illustrated. 21s.) London: Hutchinson and Co. 1954.

Mr. Kenneth Walker is well known for his writings on certain branches of medicine, and in this book he now attempts the difficult task of writing the story of medicine in a style suitable for the layman. The scope of the book extends from prehistoric medicine to the organization of the blood-transfusion service during and after the war and the discovery of penicillin. The author's style is pleasant and easy to follow, and he does not overcrowd his canvas. Up to about the beginning of the nineteenth century the story is told chronologically, but the later history is treated on a subject basis. As might be expected, the author thus finds it necessary to introduce in these later chapters accounts of the earlier history of the subjects dealt with.

Mr. Walker states the five main sources which he used in writing this book, and he quotes from them extensively. Those who know these works will appreciate that he has sometimes been unfortunate in the choice of his quotations, so that the author's meaning is distorted and the kernel of the matter is omitted. Though Mr. Walker warns the reader that there are gaps in his "story," it is rather surprising to find that his emphasis is frequently different from what one might expect. Thus, while Vesalius gets two pages, Paré gets eleven. Eight pages are devoted to Paracelsus and six to Mesmer, while John Hunter is dealt with in three. It is the rebel in medicine who seems to interest Mr. Walker most, and it is perhaps significant that this book ends with a chapter on quacks and beauty treatment.

Mr. Walker's book will be read with profit by the many laymen who show an intelligent interest in the history of medicine. It is unfortunately marred by many errors of omission and commission and by misprints. In his preface he states that he started from scratch on the history of medicine, and in six months learnt it and wrote this book. The result is interesting as the product of an acute and vigorous mind which has come fresh to the subject.

E. A. UNDERWOOD.

DIABETIC VASCULAR DISEASE

Angiopathia Diabetica: Konservative Behandlung des Zuckerbrandes. By Professor Dr. M. Bürger. (Pp. 190+ viii; illustrated. D.M. 69.) Stuttgart: Georg Thieme Verlag. 1954.

This monograph on diabetic vascular disease has as its subtitle "The Conservative Management of Diabetic Gangrene." It is pointed out that nowadays the majority of diabetics die of arterial disease, and not in coma. The author claims that there exists a specific disease of the vessels which is peculiar to diabetes mellitus. The capillaries are the important structures; they have a function in each organ that is peculiar to that organ, and that explains why in different structures capillary damage manifests itself in different ways. The retinal and glomerular lesions are referred to here. A biochemical examination of the chemical content of the vessels of normal, aged, and diabetic subjects showed that in nearly all respects the diabetics were most abnormal. Special attention is paid to the capillary resistance and other physical tests. For instance, among diabetics with albuminuria there was a much higher proportion with low capillary resistance than among those without.

These are elaborate and interesting studies. Many references are made to the literature, but it would have been helpful if more summaries and conclusions had been provided. There is a long section on the economy of physical work in diabetics. The author concludes that the metabolism of diabetics depends on uneconomical working of muscles. All this thoughtful work provides much interesting reading.

The final section deals with the bad end-results—gangrene—some 469 cases forming the basis of the author's observations. The results achieved by close collaboration with the surgeons and the help of insulin and antibiotics and sulphonamides are remarkably good, far above half the cases of gangrene being saved from amputation.

The text is well illustrated with tables, diagrams, and photographs; the print and paper are excellent.

TERENCE EAST.

CONTROL OF DIABETES

The Diabetic Life: Its Control by Diet and Insulin. By R. D. Lawrence, M.A., M.D., F.R.C.P. 15th edition. (Pp. 228+ xii. 12s. 6d.) London: J. and A. Churchill, Ltd. 1955.

Dr. Lawrence's bold experiment of writing one book for both the diabetic and his doctor has undoubtedly been a success: in 30 years 15 editions have been published. The latest contains much new material, including a very lucid description of the new insulin zinc suspensions. In this connexion it may be regretted that the Danish names for these insulins are used in preference to the approved British names.

This book is primarily intended for the general practitioner, to enable him to deal with his diabetic patients and to have some idea of what is likely to happen to them when they have to go to hospital. It does this admirably, although it is surprising to find no reference to the high incidence of coronary thrombosis in diabetics. The specialist or doctor working in hospital will also find the book helpful. The symptoms, diagnosis, complications, and treatment of diabetes are fully described. Advice on how to manage a pregnant woman or surgical patient with the condition is comprehensive and practical. The account given of the treatment of severe diabetic ketosis will not be approved by all physicians. Dr. Lawrence continues to advocate comparatively small doses of insulin in these cases, despite the figures published from Joslin's clinic in Boston. He mentions the use of potassium, but the strength of intravenous solution recommended contains a misprint which makes it difficult to interpret and the rate of administration suggested is dangerously rapid.

Two impressions remain in the mind after reading this book. The first is the debt owed to the author by all diabetics. His simplified diets, the British Diabetic Association, and his common-sense handling of everyday problems have helped diabetics in all walks of life. The second is of Dr. Lawrence's vast experience of the clinical problems of diabetes. Reference is made, for example, to 50 cases of diabetes with myxoedema and to 12 with cancer of the pancreas presenting first with diabetes. It makes one hope that one day he will find time to write a comprehensive account of the clinical aspects of this condition.

J. D. N. NABARRO.

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INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis, or glandular fever, is a puzzling disease. In the form in which it is known to-day it may well comprise a group of allied diseases. Its clinical characteristics were first outlined by Filatow and later by Pfeiffer about 70 years ago. The work of Sprunt and Evans[1] in the United States and of Tidy and Morley[2] in Great Britain did much to establish it as a clinical and haematological entity, and that of Paul and Bunnell[3] added the diagnostic precision of a serological laboratory test—agglutination of sheep red cells. In spite of these researches, however, we have not yet established the aetiology nor, indeed, a satisfactory definition of the disease. It is generally held to be an infectious disease, probably due to a virus or group of viruses, and of low infectivity as a rule, at least so far as clinical cases are concerned. Most cases occur sporadically, and it is very unusual for more than one clinical case to occur in a family or in a hospital ward. Yet a number of epidemics have been reported, generally among the staff of institutions and their immediate neighbours. The present epidemic at the Royal Free Hospital, London, is so extensive as to have had the unusual effect of compelling the hospital to stop admitting patients for a time.

Attempts to demonstrate a virus aetiology have so far failed. Transmission experiments, with one or two doubtful exceptions, have been unsuccessful. Some commentators, influenced by the resemblance of nervous and other complications—for example, meningoencephalitis and peripheral neuropathy (Guillain–Barré syndrome)—to hypersensitivity effects, have suggested a non-specific allergic aetiology. Against this is the high specificity of the Paul–Bunnell antibody test, at least in sporadic cases, and the hepatic lesions, shown by biopsy in jaundiced cases to be indistinguishable from those of acute infective hepatitis. The liver, indeed, is probably always affected in some degree, as routine tests of hepatic function in sporadic cases show.

An epidemiological feature of interest is a certain difference which seems to exist between sporadic cases and the cases in most epidemics so far reported. Shubert *et al.*[4] and Hunt[5] pointed out that in recorded epidemics the cases were nearly all clinically mild, and often symptomless except for some post-cervical glandular enlargement; the blood usually showed abnormal lymphocytes of Downey type; but the Paul–Bunnell test was frequently negative or of low titre, and adsorption tests of the heterophil agglutinin had rarely been done. These adsorption tests should be regarded as an integral part of a modern Paul–Bunnell test. The heterophil agglutinin associated with glandular fever can thus be distinguished from similar agglutinins occurring in normal persons or in persons who have recently been injected with horse serum. The former alone is adsorbed by ox red cells and not by guinea-pig kidney. Now sporadic clinical cases almost invariably yield a true positive Paul–Bunnell test, as verified by adsorption, if tested up to two weeks after onset. Moreover, some of the sporadic cases in a series of any size are severe, pyrexial, often with acute exudative tonsillitis, and sometimes with a rubelliform papulo-erythematous or even purpuric rash, appearing mainly on the trunk a few days after onset and lasting for some days. Again, the infectivity of sporadic cases seems to be low in contrast to that in epidemics. Such outstanding differences suggest some difference in aetiology between sporadic and epidemic cases. Hoagland,[6] commenting on the sporadic disease as seen in college students, noted its rare occurrence in room-mates; he found also a double peak of incidence, February and August, some five or six weeks after the end of term. In several of his cases symptoms began 33 to 49 days after an incident (usually isolated) of intimate kissing. He suggests that the virus in pharyngeal secretions may be destroyed or inhibited by dilution with saline or separation from the body (hence the failure of transmission experiments) but that it may be transmitted by intimate oral contact or by indirect transfer of saliva, as by drinking from the same bottle. His observations would suggest a much longer incubation period than the usually accepted one of five to fourteen days.

Whatever the uncertainties surrounding this disease, there is no doubt that in one form or another it is much more prevalent than is generally recognized. When a child or young adult presents with mild general febrile symptoms, or complains of tiredness in recent evenings, or of lumps or pain in the neck, or of sore throat with or without exudate coming after the onset of such symptoms, an examination for posterior cervical and axillary enlarged elastic glands and for enlarged spleen should never be omitted. An additional early sign, according to Holzel, may be a

[1] *Bull. Johns Hopk. Hosp.*, 1920, **31**, 410.
[2] *British Medical Journal*, 1921, **1**, 452.
[3] *Amer. J. med. Sci.*, 1932, **183**, 90.
[4] *British Medical Journal*, 1954, **1**, 671.
[5] *Amer. J. med. Sci.*, 1954, **228**, 83.
[6] Ibid., 1955, **229**, 262.
[7] *Lancet*, 1954, **2**, 1054.

petechial eruption along the junction of the hard and soft palate.[7] Attention may thus be directed to the underlying cause, glandular fever, rather than merely to the presenting symptom. The true history is seldom given spontaneously. The sequence of the symptoms and signs must usually be elicited by careful inquiry and examination. Sore throat, in particular, is rarely the first symptom of this disease. It is nearly always preceded by tiredness and mild illness and some swollen glands. It is probably due to the gradually developing blood condition with its low ratio of polymorphonuclear cells to lymphocytes. Exact diagnosis requires a blood count and Paul–Bunnell test.

The course of the acute disease is rarely longer than ten to fifteen days, but this may be followed by a period of weakness for some weeks and occasionally for months. Complications are relatively rare, and only a few fatal cases have been reported, death being due to hepatic or renal failure, or to rupture of the spleen, enlarged and softened as it may be by monocytic infiltration of the trabeculae. No special treatment beyond rest is indicated. Controlled experiments have shown that antibiotics are ineffectual in this disease.

SICKLING AND MALARIA

Progress in medicine is punctuated, and often accelerated, by controversy, and when A. C. Allison[1] claimed that possession of the sickling trait protected against malaria it was not to be expected that everyone would immediately accept his claim. Thus E. Beutler, R. J. Dern, and C. L. Flanagan[2] reported findings which differed from his, whereas A. B. Raper concluded from his investigations[3] that there is enough evidence to give support to Allison's hypothesis. Previously, R. A. Moore, W. Brass, and H. Foy[4] stated that their results gave "no confirmation of the theory . . . suggested by Allison," but G. M. Edington,[5] after describing his observations on the same subject, stated: "These results are as yet inconclusive and further work will require to be done. However, the general trend of the figures is in agreement with those of Allison." The time appears to be ripe for re-examining the views of the opposing parties and for attempting to mediate between them.

The main observations made by Allison[1] were that the incidence of malarial parasitaemia in 43 Ganda children with the sickle-cell trait was significantly lower than in a comparable group of 247 children without the trait. When 15 males of the Luo tribe who did not possess the sickling trait were experimentally inoculated with *Plasmodium falciparum*, 14 developed an overt infection; but when a similar number from the same tribe but possessing the trait were inoculated only 2 developed an overt infection. He emphasized that his observations indicate that "natural resistance to malaria among individuals with the sickle-cell trait is relative, not absolute. . . . However, even a relative resistance to malaria may be enough to help those with the sickle-cell trait through the dangerous years of early childhood, during which an active immunity to the disease is developed." He concluded that "abnormal erythrocytes of individuals with the sickle-cell trait are less easily parasitized by *P. falciparum* than are normal erythrocytes," also suggesting that "protection afforded by the sickle-cell trait is more effective against *P. falciparum* than against other species of plasmodia."

The principal evidence brought forward against this hypothesis is that Moore and his colleagues examined two neighbouring communities in which the incidence of the sickle-cell trait differed and yet the incidence of malaria was almost identical. They also compared the sickling rates in parasitized and unparasitized persons in these two communities and again found similar figures in each. The work of Beutler and his colleagues may at first seem to show that Allison's original experiment on the transmission of malaria to sicklaemics has now been repeated and that his findings have not been confirmed. However, this is not so, for in spite of the conclusions drawn they found in one experiment that "it was necessary to interrupt infection of three of the 'non-sicklers' before it was necessary to interrupt the infections of any of the 'sicklers'"; and in a second experiment they also found treatment to be required by two of the three non-sicklers before it was required by any of the sicklers.

The protection afforded by sickling has never been claimed to be absolute, but when augmented by some degree of naturally acquired immunity it may be sufficient to prevent infection or to make infection light and transient. The latter possibility renders the criticisms of Moore *et al.* of less importance than at first they seem to be. Their survey covered persons of all ages, and the naturally acquired immunity possessed by adults is apt to obscure the protection afforded by the sickle-cell trait. This protection is more clearly shown by surveys—such as Allison's—limited to children, and still more clearly by parasite counts in children, as was strikingly illustrated by Raper.[3 6] Erroneous conclusions are likely to be drawn from surveys in which no account of the age of the patient is taken.

[1] Allison, A. C., *British Medical Journal*, 1954, 1, 290.
[2] Beutler, E., *et al.*, ibid., 1955, 1, 1189.
[3] Raper, A. B., ibid., 1955, 1, 1186.
[4] Moore, R. A., *et al.*, ibid., 1954, 2, 630.
[5] Edington, G. M., ibid., 1954, 1, 871.
[6] Raper, A. B., ibid., 1954, 2, 1162.

Important evidence in this controversy is published in the *Journal* this week (p. 301) by Drs. G. A. Deliyannis and N. Tavlarakis. They are fortunate in that there is a Department of Malaria in Northern Greece in which records of patients suffering from malaria are kept. By using these records it was found that the mean rate of sickling in persons suffering from malaria in the area was only 5.8%, whereas in 500 unselected local inhabitants used as controls the rate was 23.6%. A very interesting study was also carried out in which blood from the members of the families of those who had malaria was examined for sickling and for the presence of malarial parasites. With but a single exception those whose blood sickled were found to be free from malaria, and those with malaria did not possess the sickling trait. The authors conclude "that the co-existence of malaria and sickling is of a low order. Sicklers show a stronger resistance against the infection." It is possible that the reason why these results are more clear-cut than those obtained from similar studies in Africa is because malaria in Northern Greece is not now as highly endemic as it is in tropical Africa. Naturally acquired immunity is therefore less likely to obscure the protection against it which is afforded by possession of the sickling trait.

Deliyannis and Tavlarakis have also carried out a survey of the incidence of sickling in Northern Greece, reported at p. 299. They covered thirty-seven villages, and in twenty-two of them people with the trait were found. It is of interest and importance to note that the region in which these villages are situated is one in which before the last war malaria was hyperendemic. The authors attempt to deduce that the sickling trait has not been imported into Greece from Africa, but has arisen locally as a result of gene mutation. Here they enter another highly controversial field. The point is made that the population in which sickling occurs, and the families of many of those affected, have been in the region for several centuries. This, however, does not exclude the possibility of immigration of persons of negroid stock several centuries ago, and on geographical grounds such immigration from time to time would appear probable. If it did occur, Allison's hypothesis is supported by survival of the gene in an area which, until recently, was hyperendemic for malaria, for this is exactly what might be expected if possession of the trait diminishes mortality among infants infected with malaria.

The argument continues, but meantime the point appears to have been established that possession of the sickle-cell trait affords some protection against infection with *P. falciparum*, usually causing the infection to be of shorter duration and to be associated with lower parasite counts than in people who do not possess the trait. Important biochemical studies are likely to develop from this work, and among these will be a comparison of the ways in which malaria parasites metabolize normal haemoglobin (haemoglobin A) and sickle-cell haemoglobin (haemoglobin S).

REACTIONS TO PENICILLIN

In freedom from toxicity penicillin is a unique drug; to all animals except the guinea-pig it is no more toxic than sodium chloride. There are nevertheless risks involved in its use which from their nature and undoubtedly increasing prevalence are causing some alarm. These depend on sensitization, usually by previous administration, although contact with other fungal products or fungi is said sometimes to have a similar effect, and the tendency to react abnormally is certainly greater in asthmatics. That sensitization can occur was recognized fully ten years ago, but the effects reported then were of the serum-sickness type—fever and urticaria or other skin rashes. For some reason not fully explained a much more serious type of reaction has been generally reported only within the past three years: this is a vasomotor collapse of immediate onset, which has been described as anaphylactic shock, not infrequently fatal within a few minutes of the injection being given. Drs. R. J. Calvert and E. Smith report another example of this at p. 302 which is rather atypical in that the onset was apparently delayed for 15 minutes: they also review some of the now voluminous literature of this condition and suggest precautions by which the risk of its occurrence can be reduced.

The first of these precautions is obviously to limit the use of penicillin to patients who really need it. In the United States, where its use has been much more lavish and indiscriminate, sensitization is far commoner and the whole problem more serious. Thus S. Swift[1] records that the case sheets of 82 out of 778 patients attending a clinic in New York in one week were stamped "Allergic to penicillin." The survey by H. Welch and his colleagues[2] probably does not reflect the true present frequency of severe reactions, for P. S. Mayer and his colleagues[3] describe six cases apparently in their own practice in Hines, Illinois, and M. M. Halpern and B. Ross[4] collected accounts of eleven "by random questioning of

[1] *Lancet*, 1954, **2**, 602.
[2] *Antibiot. and Chemother.*, 1953, **3**, 891.
[3] *J. Amer. med. Ass.*, 1953, **151**, 351.
[4] *Sth. med. J. (Bgham, Ala.)*, 1954, **47**, 1085.
[5] *Arch. Derm. Syph. (Chicago)*, 1950, **62**, 314.
[6] *Antibiot. and Chemother.*, 1952, **2**, 385.
[7] *British Medical Journal*, 1954, **1**, 500.
[8] *Arch. Derm. Syph. (Chicago)*, 1953, **68**, 323.
[9] Ahnefeld, F. W., *Med. Klin.*, 1954, **49**, 1480.
[10] Berry, C. Z., and Ferber, J., *U.S. Armed Forces med. J.*, 1954, **5**, 1137.
[11] *Lancet*, 1954, **2**, 1157.
[12] *Med. J. Aust.*, 1953, **2**, 820.

approximately fifty physicians practising in the Miami area." In guarding against reactions when penicillin has to be given, the simplest precaution, and one which should never be omitted, is to inquire whether the patient has experienced any abnormal effects from the drug before. When the danger is known to exist it can easily be averted. S. W. Simon and M. D. Feldman[5] and L. Maslansky and M. D. Sanger[6] have shown that admixture with an antihistamine compound enables penicillin to be given safely to sensitized patients. H. W. Balm and A. E. Dormer[7] were able thus to initiate the treatment of a patient with subacute bacterial endocarditis who had reacted violently to the drug before, and a few days' administration under this cover desensitized her. L. J. Alexander[8] has also shown that deliberate desensitization without antihistamines is feasible. There is even a proprietary form of penicillin,[9] known in Germany as "neopenyl" (to be distinguished from "neopenil," a quite different substance), which is a combination of the antibiotic with an antihistamine.

It is more difficult to say what routine precautions are indicated in addition to simple inquiry and special care in treating asthmatics. The means of combating a dangerous reaction should of course always be readily available, and were they applied instantly fatalities would probably be rare. It should be verified that the needle is not in a vein before an injection is given, although the frequency of accidental intravenous injection as a factor is still uncertain and calls for closer investigation. It may be asked whether the possibility of such reactions should influence the choice of compound and route of administration. The oral route has been recommended on this account, but is not entirely free from risk, as is shown in Calvert and Smith's own case. C. Z. Berry and J. Ferber[10] report reactions in 0.3% of 33,827 men given a small dose of penicillin orally for 5 or 10 days. More exact information is needed on the relative degrees of danger associated with soluble and procaine penicillin, and on whether sensitivity to procaine itself is a factor. Even more insoluble forms can be particularly dangerous owing to their long-continuing action: in the case described by H. C. Anderson[11] a single intramuscular dose of benzathine penicillin produced appalling effects progressing for four days, but then fortunately terminated by cortisone. It has been seriously suggested that injections should always be given into the arm, so that a tourniquet can be applied if necessary: to make this a general rule would scarcely be feasible. Skin tests of sensitivity have been condemned on the ground that they themselves are unsafe. This is not true of the scratch test, but according to P. W. Farmer[12] they are also unreliable, since sensitized patients sometimes fail to react. It is probable that any dangerously sensitized subject would react, although this also needs verification, but the main fact about such tests is that they are simply not practicable as a routine procedure. Those who have to prescribe penicillin need to be aware of all these facts, and further experience will doubtless lead to the formulation of a policy combining caution with reasonable simplicity in execution.

HALLUCINATIONS OF THE SELF

The strange experience of seeing a hallucinatory vision of oneself, the so-called autoscopic or heautoscopic hallucination, has always aroused in medical men rather more interest than its actual clinical significance warrants. Perhaps the interest is partly literary in quality, and depends on the appeal of the eerie, echoing the Doppelgänger of folklore.[1] Normal people have experienced something of the kind in circumstances of fatigue or exhaustion; and, according to K. Conrad,[2] descriptions of such visions have been given by Goethe, Maupassant, and Dostoevski.

A noteworthy contribution to the sparse literature on this out-of-the-way corner of medicine has recently been supplied by K. Dewhurst and J. Pearson.[3] They describe three cases. In the first of these an intelligent man of 46 had a subarachnoid haemorrhage. The first symptom of the trouble, and the only one for the first two days, was that of seeing himself "quite solid, as if seen in a mirror." The apparition was dressed exactly as he was, and accompanied him everywhere. "At meal-times it stood behind his chair and did not reappear till he had finished eating. At night it would undress and lie down on the table or couch in the next room of his flat. The double never said anything to him or made any sign, but only repeated his actions: it had a constant sad expression." Though the patient was fully aware that it was a hallucination, he felt impelled to draw up a chair for it when he first visited his private doctor. In the second case the patient, who had a haemorrhagic tumour in the left occipital lobe, was a less intelligent man; and he saw the same figure for a number of days before at last recognizing it, with an access of fear, as himself. In the third case, a man of 57, similar experiences occurred as epileptic phenomena associated with a foreign body in the right temporal lobe. The first of these patients is also discussed in some detail by W. Ritchie Russell and C. W. M. Whitty,[4] who add yet another case of traumatic epilepsy involving experiences of a psychologically similar kind: in his attacks the patient felt detached from his own body and able to look at it from outside. Further by-ways are explored by Dr. Macdonald Critchley in an article at p. 284 of the *Journal* this week, in which he discusses disorders of the body image. He draws attention particularly to the individuality with which hemiplegic patients may

[1] Lhermitte, J., *British Medical Journal*, 1951, **1**, 431.
[2] Conrad, K., *Encéphale*, 1953, **4**, 338.
[3] Dewhurst, K., and Pearson, J., *J. Neurol. Neurosurg. Psychiat.*, 1955, **18**, 51.
[4] Russell, W. R., and Whitty, C. W. M., ibid., 1955, **18**, 79.
[5] Hill, D., and Mitchell, W., *Folia psychiat. (Amst.)*, 1953, **56**, 718.

endow a paralysed limb. "The crippled and useless limbs are referred to as though invested with a personality or identity of their own . . ." and often given half-facetious names.

In an excellent review of the subject Conrad[2] classifies autoscopic experiences in three groups. In the first we have the phenomena occurring in normal persons. Here consciousness is always modified, being dreamy and close to sleep; the hallucination is momentary, more visionary than visual, and is seen, according to Goethe,[2] "plus avec l'œil de l'esprit," or, according to Conrad, more cynically, "avec l'esprit du poète." In the second group we have the autoscopic experiences of the mentally ill, the delirious or the schizophrenic; and in these cases again there is some alteration of consciousness. It is probably in this group that belong those cases, discussed by Dewhurst and Pearson, in which the symptom can be attributed to disturbance of basal areas of the brain by toxic-infective processes. From both of these groups Conrad sharply distinguishes a third, in which the visual experience is precisely characterized and recurs always in identical form—that is, the vision of oneself "as if in a mirror." To this subgroup alone of all autoscopic experiences he allows the title of the mirror hallucination. In his paper he reports a personal observation of a man with a tumour of the hypophysis which brought about blindness in the course of some years; eight days after the blindness became complete, a vision of his own face appeared and has persisted undeviatingly a metre in front of him for seven succeeding years. Conrad likens the phenomenon to that of the phantom limb, here transferred to the visual from the kinaesthetic field, and he would therefore be at one with Dewhurst and Pearson in including the symptom among the disturbances of the body image.

Conrad emphasizes that everyone who can see knows well the sight of his own face and person; it is less surprising that such an object should appear in a hallucination than that it should do so only rarely. It is a significant feature of the autoscopic hallucination, at least when it is caused by a focal lesion, that it is, apparently invariably, seen "as if in a mirror." The suggestion arises that the form of the hallucination depends on the activation of pathways which involve visual memory traces. D. Hill and W. Mitchell[3] have recently drawn attention to the re-living in an epileptic aura of past actual experience, or the involvement of memory in hallucination. Hallucinations of the self may also appear in an epileptic aura, and of the cases described in the literature a considerable proportion were caused in this way. In the cases reported by Hill and Mitchell the focus of origin of the epileptic fit was in a temporal lobe. A temporal origin might also be assumed or suspected in many of the patients who have had the mirror hallucination, as, for instance, in those described by Dewhurst and Pearson.

Neurological explanations, therefore, attribute the cause of autoscopic hallucinations to irritation of parts of the brain which are known to give rise, when disturbed, to complex hallucinations. Dewhurst and Pearson do not think this explanation is quite sufficient: among other things, the relative rarity of autoscopic hallucinations remains unexplained. They draw attention to the great individual variation in the general capacity to visualize, or to retain memories in visual form; and they suggest that there are people who possess, more than others, the "faculty of seeing a spatially localized mirror image of themselves," and that it is among them that a focal organic lesion may produce the phenomenon of autoscopy. This suggestion could be confirmed or refuted by further observation.

SMALL CHILDREN IN HOSPITAL

A joint committee of the Institute of Child Health (University of London), the Society of Medical Officers of Health, and the Population Investigation Committee has been finding out how many children of pre-school age are admitted to hospital, and why. According to the committee's recently published report[1] the annual rate of admission to hospital during the first five years of life, on the basis of the sample taken, was 53.0 per 1,000 children (this figure omits admissions during the first month of infancy, which are difficult to interpret). Nearly half the children who went to hospital stayed for one week or less; only one-third stayed longer than a fortnight. The main causes of admission were, in the first year, congenital malformations, digestive diseases, and lower respiratory infections. By the age of 2 tonsillectomies began to account for one-quarter of the admissions, and bacterial infections for a further 10%. The admission rate for boys was higher than for girls in each year of life, mainly on account of the high rates for congenital malformations (in the first year only), digestive diseases, circumcision, and accidents. Children from manual workers' homes had a significantly higher rate of admission for infections than those from homes where the father belonged to the professional class or was a black-coated wage-earner. As regards other disorders there were no marked social differences, except for the small group of unskilled manual workers' children, who had a consistently high rate of admission for all causes except tonsillectomy, which was low. The report states that the apparently greater incidence of infections among manual workers' children was due partly to the prevalence of large families—with the risks of infection by contact with schoolchildren—and partly to the greater overcrowding in these homes. Children from large families were nearly twice as likely as only children to be admitted for infections.

This survey of child health, some of the results of which have been given in earlier publications, started in 1946, when women in all parts of the country who had given birth to a child during the first week in March of that year were seen by health visitors and asked questions about their pregnancy and confinement. The growth and health of the children born during that survey week have been followed, but the original group proved unmanageable in numbers, and was reduced by taking a random sample of one out of every four children whose fathers were manual workers: all the

[1] "An Account of Hospital Admission in the Pre-school Period," obtainable from the Secretary of the Joint Committee, 13, Endsleigh Street, London, W.C.1.

[2] See *British Medical Journal*, 1953, 1, 609.

children of parents in other occupations were retained in the survey. So far as pre-school children are concerned, the hospital admission figures quoted above relate to the period 1946–51, and later developments may have modified the conclusions to be drawn. For example, a section of the report deals with the question of hospital visiting. One-third of the children were admitted to wards which allowed no visitors, and it is probable that fewer wards to-day enforce such a cast-iron rule. In 1953 the Central Health Services Council gave its blessing to the daily visiting of children in hospital by their parents, and the Ministry of Health sent out a circular urging this on local authorities, with adequate safeguards against the introduction and spread of infection. Even during the years 1946 to 1951 some parts of the country were much more enlightened than others. Scotland was only half as strict as Newcastle-upon-Tyne in enforcing the no-visiting rule. In Sheffield only 24.6% of wards enforced the rule, whereas in Birmingham the corresponding figure was 59.7%. In Oxford the no-visiting rule prevailed in only 15.6% of wards, whereas in East Anglia it was in force in over 39%. Recent correspondence in the national press shows that there is still much public uneasiness about the attitude of some hospitals in not allowing children to be frequently visited by their parents, and it is worth recalling that the Hospital for Sick Children, Great Ormond Street, is strongly in favour of mothers visiting their children daily between 5 and 6 p.m. so that they can help the nurses at the children's bedtime.[2]

BLOOD COAGULATION IN OBSTETRIC EMERGENCIES

In pregnancy a haemostatic defect may develop from disturbances of blood coagulation. This haemorrhagic state, arising in some obstetrical emergencies, has been recognized for many years but has recently received renewed attention, and is the subject of two papers in this week's *Journal*. The coagulation abnormality is most commonly seen in association with accidental antepartum haemorrhage,[1] but, as Dr. J. S. Scott (p. 290) and Dr. A. P. Barry and his colleagues (p. 287) point out, it can also occur in amniotic fluid embolism, in association with retention of a macerated foetus in an Rh-immunized mother, in missed abortion, and in hydatidiform mole. The exact nature of this clotting defect is not clearly understood, but two changes have been accepted as features of the condition—deficiency of fibrinogen and an active fibrinolytic system. Some believe that the depletion of fibrinogen is due to excessive utilization as a consequence of intravascular clotting or of the formation of retroplacental clot or of fibrin deposition in the uterine wall; others suggest that it is a result of abnormally active proteolytic systems in the blood, causing fibrinolysis or possibly fibrinogenolysis.

The theory which has gained most support is that of C. L. Schneider,[2–4] who believes that tissue thromboplastin is liberated into the circulation as a consequence of the disruptive process in the uterus and that this initiates intravascular clotting. The resultant fibrin forms multiple minute emboli in the pulmonary and other capillary beds, and the patient may die because of the fibrin in the pulmonary arterial tree, or there may be depletion of fibrinogen with resultant failure of blood clotting. There is some experimental evidence in favour of this theory. The injection intravenously in animals of tissue thromboplastin causes fatal intravascular coagulation or a clotting defect which is characterized by a depletion of fibrinogen. It has been suggested that the fibrin thrombi in the kidney in renal cortical necrosis accompanying severe accidental haemorrhage may be a manifestation of this hypothetical liberation of thromboplastin into the circulation. On the other hand, Sheehan and Moore[5] maintain that the thrombi may be secondary to vascular renal damage caused by transient vasoconstriction.

Similar disturbances of blood coagulation have been reported in conditions other than pregnancy, including lung operations, multiple gunshot wounds, prostatic disease, and pancreatic tumours. In the lung operations and gunshot wounds release of thromboplastin into the circulation seems again the likely cause; in prostatic disease and pancreatic tumours release of fibrinolytic enzymes might be responsible.

When defibrination of the blood has been complete the recognition of the condition is easy, since the blood is incoagulable. Unfortunately there may be just sufficient fibrinogen for *in vitro* tests of the coagulation time of whole blood to be normal. It is therefore important in obstetrical emergencies to have methods for the estimation of fibrinogen readily available. The reliable estimation of fibrinogen is difficult, the Kjeldahl method being probably the most accurate, but requiring several hours. The authors of the two papers in this issue both describe rapid methods of fibrinogen determination.

There may be many patients requiring treatment for obstetric emergencies in whom fibrinogen depletion is insufficient to cause clinical signs of a haemostatic abnormality. Scott suggests that the administration of dextran may be responsible for haemorrhage in such patients. Dextran has been reported to cause transient thrombocytopenia and also to be capable of inactivating fibrinogen by the formation of a dextran-fibrinogen compound which may precipitate. This latter effect could, in those patients suffering from obstetric emergencies, reduce the fibrinogen further, to a level at which abnormal haemorrhage might occur. Scott therefore justifiably recommends that plasma should be preferred to dextran when resuscitative treatment is necessary for conditions in which hypofibrinogenaemia is apt to develop.

Mr. Charles David Read, director of the Institute of Obstetrics and Gynaecology, University of London, was elected President of the Royal College of Obstetricians and Gynaecologists on July 23. The two Vice-Presidents are Professor A. M. Claye and Mr. V. J. F. Lack.

[1] Barry, A. P., Feeney, J. K., and Geoghegan, F. J., *British Medical Journal*, 1955, **2**, 12.
[2] *Surg. Gynec. Obstet.*, 1951, **92**, 27.
[3] *J. Obstet. Gynec.*, 1951, **58**, 538.
[4] *Amer. J. Obstet. Gynec.*, 1952, **64**, 141.
[5] *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage*, 1952, Oxford.

EMERGENCIES IN GENERAL PRACTICE

SENILE CONFUSION

BY

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Senile confusion may give rise to an emergency in general practice in one of two quite different ways: a call is received, usually at night, because an old man or woman has suddenly begun to behave in a highly disturbing and sometimes dangerous fashion, on account of an acute senile confusional state; or, in the course of long-standing senile mental deterioration, a medical, psychological, or social situation has arisen suddenly, demanding immediate action. An acute senile confusional state is often, though by no means always, a complication of chronic senile confusion, which may therefore be discussed first.

Chronic Senile Confusional States

This term is used here to label the all-too-familiar clinical picture of a senile and ill-cared-for person, with a bewildered expression, moving about in a vague and aimless fashion, and only dimly aware of his or her whereabouts. While still able to recognize his relatives, he may misidentify less familiar figures like the doctor, and even on the briefest mental examination he will show obvious defects of memory and other intellectual functions. However, some patients with senile mental deterioration make a bright and alert impression superficially, and look deceptively healthy and younger than their years. But even brief contact will reveal behind a preserved ability to utilize a few conversational gambits a mind as empty as a shell. Inquiries into memory of recent, and sometimes even remote, events of a personal or more general nature tend to be evaded by proffering various excuses, or there may be a tendency to fill memory gaps with accounts of imaginary events.

Emergencies in Chronic Senile Confusion

These persistent states of mental confusion, which are usually due to global senile degeneration of brain cells or to ischaemic softening of large areas of the brain, the physical bases respectively of senile and arteriosclerotic dementia, may create acute problems of management in several ways. In addition to intellectual and personality deterioration, some patients may show episodic mental disturbances; mood changes are fairly frequent, but they are usually labile, short lasting, and only rarely culminate in attempts at self-injury. More common are persecutory episodes, delusions of theft, of poisoning, of not being wanted, or of poverty. When called on to deal with such an acute mental disturbance the doctor on arrival will usually find that the episode has blown over, and a hot drink, together with a quickly acting barbiturate such as pentobarbitone sodium, 1½–3 gr. (0.1–0.2 g.), may be all that is required to restore the domestic peace.

There are, however, features other than frequent recurrence of psychotic episodes which may lead not, perhaps, to strictly medical emergencies but to equally urgent social ones: wandering away, incontinence, hoarding and collecting rubbish, constant restlessness, and getting up at night, often under the impression that it is time to go to work (many years after retirement)—these are only a few of the aberrations and behaviour disorders which may place an unbearable strain on the patient's friends. Most workers in the geriatric field are agreed, in spite of the publicity given to hard cases, that the overwhelming majority of people continue to look after the mentally and physically infirm members of the older generation with considerable affection and self-sacrifice. But suddenly they may reach breaking point, and the family doctor is called in and faced with demands for immediate relief of a situation which has become unbearable.

The taking of a full history and the conducting of a thorough physical and mental examination of the patient are not only essential for reaching a sound decision but will also have the effect of calming the family crisis which has led to the emergency call: realizing that considerable trouble has been taken, the relatives may more easily accept the assurance that relief will be procured, but that making suitable arrangements may take a little time.

Psychological Factors

It is important to remember that not all mental disturbances during the senium are due to senile or arteriosclerotic dementia. Depressive illnesses are quite common in old people and respond well to modern forms of psychiatric treatment. Such elderly depressed patients often do not present with tears, guilt, self-reproach, and retardation, but with agitation, panic, perplexity, and persecutory delusions and hallucinations. It may be quite difficult to distinguish the puzzled and aimlessly restless senile dement, who believes himself impoverished or poisoned, from the agitated, bewildered melancholic plagued by imaginary voices. It is equally difficult to exclude the presence of intellectual impairment in mentally ill persons. The doctor is likely to find that the history of the development of these disturbances contains the most helpful diagnostic pointers.

In senile psychotic states there will always have been a prodromal period of some months or years during which failure of memory, of general abilities, and of personal adjustment has been noticed, though leading questions may have to be put to the informants to elicit the state of affairs. Positive evidence to show that until a few weeks or months ago the patient had been well preserved in his mind, fully capable in his sphere of activity, and retaining a good grasp on what was going on around him points to a sudden mental reaction which is only occasionally associated with important physical changes in the brain. If the practitioner suspects that he is not just dealing with an acute disturbed episode in the course of senile deterioration, he should advise psychiatric consultation, and, if a fairly hopeful prognosis is given after it, persuade the family to accept mental hospital treatment for the patient.

Physical Factors

Assessment of the physical state may yield important pointers towards correct management. While the routine treatment of senile deterioration with vitamins has, on the whole, been disappointing, from time to time patients show clear evidence of hypovitaminosis in the form of angular stomatitis, undue tendency to bruising, or dermatitis of exposed skin surfaces (not to be confused with skin pigmentations so often seen in old people).

Neurological examination may produce evidence of the same intracranial disorders as may be associated with mental symptoms in younger people—for example, tumours or general paralysis of the insane, by no means so very unusual in people over 60. A more frequent cause of abnormal neurological finding is cerebral thrombosis, and if there is a history of a recent stroke or "strokelets" there is always a fair chance of an early remission of

any concomitant mental symptoms. Abnormal neurological signs in the extremities, especially reflex abnormalities, and absence of vibration sense in the lower limbs as well as the presence of paraesthesiae are common in elderly people, but, by failing to arrange for full blood examinations, many cases of subacute combined degeneration with varying degrees of macrocytic anaemia are probably overlooked in this age group.

In a recent personal case simultaneous restoration of the blood picture and remission of the mental symptoms, which were quite non-specific, were achieved only when daily injections of 100 μg. of vitamin B_{12} were given. A suspected case should be referred to a geriatric or medical specialist for diagnostic and initial treatment. If in the presence of any of these physical disorders, or marked cardiac failure or respiratory infection, the services of a trained nurse cannot be made available, determined efforts should be made to obtain the patient's admission to hospital or nursing-home, with a physical diagnosis. Nocturnal restlessness, hallucinations, or persecutory preoccupations tend to disappear very quickly with suitable treatment of physically ill, and often neglected, old people; admission of such cases to a mental observation ward or directly into a mental hospital should be avoided.

Social Factors and Management in the Home

In a large proportion of cases neither the physical nor the mental condition of the elderly person may demand or justify admission to a hospital, and yet a situation is often found where family care appears to have broken down. There is no doubt that, except in the last stages of dementia, patients are happiest in their own homes, and removal from familiar landmarks by admission to hospital or institution is a well-known cause of acute confusional episodes. Many people are quite unaware of the existence in their locality of home nursing services, sitters-in, and laundering arrangements, and the use of these facilities may often enable families to go on looking after their aged invalids with restored morale. The family doctor should be familiar with the services for old people available in his area through contact with the medical officer of health, the local old people's welfare committee, and similar voluntary bodies; he may also find at his disposal a domiciliary geriatric consultant service.

Nocturnal confusional episodes may sometimes be avoided by a dimmed light in the bedroom. For mild behaviour disorders and nocturnal restlessness a variety of drugs have been recommended and may be given a trial. It has recently been claimed that an elixir containing leptazol and nicotinic acid might make it possible for many deteriorated and mildly disturbed old people to continue life with their families. The formula is as follows: Leptazol, 0.2 g. (a dose which is likely to evoke protests from the dispenser); nicotinic acid, 100 mg.; elixir pepsin (*B.P.C.*), 1 fl. dr. (3.5 ml.), three times a day. Personal experience with this mixture has so far proved inconclusive. The use of chlorpromazine has been reported as disappointing in three cases of senile psychosis. Caffeine citrate, 5 gr. (0.32 g.), or a cup of strong coffee or tea at night has sometimes been helpful. Claims have recently been advanced for the efficacy and low toxicity of methylpentynol in the treatment of nocturnal restlessness in senile patients. It may be administered in capsule form or as a draught. May and Ebaugh suggest an initial dose of 0.5–1 g., which, if ineffective, may be increased by 0.25 g. every other night. They did not find it necessary to increase the dose beyond 1.75 g. in any mental hospital senile psychotic over 70.

In many instances the material circumstances of the home will make continued family care impossible, or the doctor may find that there is a definite threat to the health of the person carrying the burden. In cases of this kind the practitioner should be able to advise on suitable homes which are to be found in most areas: a uniformly high standard of care would no doubt be encouraged if doctors were to recommend only homes which they had inspected personally. Unfortunately, in many localities it will be found that, in view of inadequate general hospital facilities for infirm and confused elderly patients, admission to a mental hospital may be the only way of obtaining adequate care.

Acute Senile Confusional States

While emergencies due to the type of senile confusion so far discussed are largely avoidable by attending early to the patient's physical, psychological, or social situation, actual or impending, acute senile confusional states may arise quite unexpectedly. Although brief confusional episodes, especially at night, are common in old people, what now must be considered are severe delirious states which may continue for several days or even weeks. The prognosis is grave, the condition being terminated by death in about half the cases. Every practitioner will be familiar with these delirious pictures: a restless, frightened patient, muttering, aimlessly groping, bewildered, disorientated, and often responding to vivid visual hallucinations. A considerable proportion of patients who survive the delirious state return to good mental health and may not develop any senile mental deterioration in the next few years. Thus the successful treatment of an acute senile confusional state may be followed by the same gratifying results as skilled medical or surgical treatment of physical emergencies in old age. As with them, treatment must begin at once, and high-quality nursing is required. The task of the family doctor is twofold: (1) to support the patient during the first and most important few hours; and (2) to obtain speedy admission to a suitable hospital.

First and foremost the general practitioner will have to convince himself and the admitting medical officer that he is really dealing with an acute delirious reaction and not with the terminal delirium of a mentally deteriorated or physically cachectic patient. This may be a very difficult matter, unless from personal knowledge or a reliable history it seems quite clear that until a day or two before the sudden manifestation of mental confusion the patient had been well adjusted and with good memory and grasp of his surroundings. Where there is any doubt of the reliability of the informants, a full description of the patient's activities a day or two earlier should yield the true picture of his recent psychological status.

But the doctor may be called to see severely confused lonely old people with hardly any history available; under these circumstances he will have to rely on an interpretation of the clinical state along the lines suggested in the valuable chapter on mental diseases of the aged in Mayer-Gross, Slater, and Roth's *Clinical Psychiatry*. Patients who have been mentally well until quite recently will usually have a well-preserved and well-cared-for appearance; in a truly acute delirious episode there will occur from time to time lucid intervals due to fluctuations in the state of awareness, and during these moments of mental clarity the patient will show little or no memory disturbance except perhaps for very recent matters. During an acute disturbed episode in the course of a long-standing dementia old people will not show any lucid intervals, and will be evasive and vague in their replies to questions referring to memory or orientation. By contrast, the recently confused patient will give positive answers but will remain quite unaware of the fact that his statements are inconsistent and contradictory. Delirious pictures may also be seen in patients with rapidly developing severe depressive and agitated psychoses demanding speedy transfer to psychiatric care; the history will usually yield some evidence of prodromal affective change, and fragments of the patient's thought content pointing to a primary mood disturbance may be obtainable.

In many instances patients recover from acute senile confusional states without any adequate physical cause ever having been discovered, but in most cases there is evidence of important precipitating physical factors. These may be obvious in spite of the difficulties of examining a severely disturbed and restless patient. There may be neurological signs pointing to cerebral incidents or neoplastic deposits,

or signs of severe cardio-respiratory failure. But it is well known that severe confusional states may be facilitated in elderly people by mild infective conditions such as those of the urinary tract, small areas of pneumonic consolidation, or thrombophlebitic patches in the legs. The possibility of a drug intoxication should always be remembered.

Management of Acute Confusional States

After ordering the appropriate initial treatment for any physical disorder present, adequate and speedy sedation should be aimed at in order to conserve the patient's strength. If the condition is not very severe, rapidly acting barbiturates may be given a trial; pentobarbitone sodium, 1½–3 gr. (0.1–0.2 g.), or quinalbarbitone sodium, up to 3 gr. (0.2 g.), are recommended. But inadequate repeated sedatives are often harmful by producing additional befuddlement, and as an initial hypnotic paraldehyde is to be preferred. Administration by mouth should be attempted at first with haustus paraldehydi *N.F.* in doses of 1½–3 fl. oz. (43–85 ml.). Only when the patient refuses the draught should intramuscular injection be resorted to, and for this injectio paraldehydi *N.F.* in a dose of 5–10 ml. is indicated. It is claimed by workers with extensive experience that abscesses are only very rarely produced if the injections are given deeply and into the vastus lateralis rather than into the gluteal region. With the patient sedated, a second physical examination may reveal the presence of disease which went undiscovered a few hours earlier, and this will lead to renewed efforts at securing the patient's admission to the medical or surgical wards of a general or geriatric hospital.

On the other hand, a regime of sedation may render the admission of patients with terminal confusional states to mental hospital or observation wards unnecessary. When admission to hospital is delayed, the practitioner, as well as treating any physical disease present, may consider giving intravenous glucose injections. It has been claimed that with this treatment, the rationale of which is not at all clear, a much higher recovery rate is achieved in the toxic delirious reactions of old age than with a regime of sedation. Infusions of 10% glucose in normal saline for the first few days, and later in sterile water, are recommended. One to two litres should be given daily during the first few days, later only 500 ml. a day, and the rate should never be more than 50 drops a minute.

Next article on Emergencies in General Practice.—"Gassing in the Home," by Dr. A. Thelwall Jones.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

The Victoria Cross awarded to Assistant Surgeon Thomas Egerton Hale, which was recently sold at Christie's for the record price of £420, was the first V.C. ever awarded to a member of the medical profession. The deed which earned it was performed on September 8, 1855; it was gazetted on May 5, 1857, being a retrospective award, as the V.C. was not instituted until January, 1856. Surgeon James Mouat was later awarded the V.C. for a deed performed on October 26, 1854 (see *Journal*, 1954, **2**, 1045).

SOCIOLOGICAL IMPLICATIONS OF DIABETES*

BY

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Had I been asked ten years ago, "What are the sociological problems of diabetes?" I would have replied vaguely, "I do not know; are there any?" It was not until I worked with a group of diabetics in a clinic that my attention was drawn to some of their personal conditions, and the lack of means to redress their wrongs, which awoke in me a sense of their necessity and a need for a different approach.

This paper does not set out to be a complete survey of the sociology of diabetes—this was done admirably by Professor Tunbridge (1953) in his Banting Memorial Lecture at Leeds—but the substance of my personal experience. One of my earliest social problems is described in the following case record.

A Problem Case

Jane had become diabetic at the age of 13, in 1942. She lived in a very poor district and had no stability at home. She was labile and readily passed into ketosis and coma. An added misfortune was that she suffered continual dermal reactions to insulin, and as she was not very clean these lumps often became abscesses, which increased her insulin requirements. She did not like coming to the clinic: she thought our standards were too high.

In 1948 Jane was admitted to hospital with a pleural effusion which was concurrent with an early pregnancy, so she took her own discharge and got married. At about the 38th week of pregnancy she was admitted to another hospital in toxaemia. Induction of labour was performed by rupture of the membranes, and after a difficult forceps delivery the child, a boy, lived, and so far as I know is still alive. Jane, however, was transferred to the Isolation Hospital on account of septicaemia and rapidly spreading bilateral pulmonary tuberculosis. She required over 100 units of insulin a day and was treated with penicillin and streptomycin. I did not enjoy my weekly visit to her: she was ungrateful, discourteous, and uncooperative. In October, 1949, pneumoperitoneum and phrenic crush were performed, and in May, 1950, a tuberculomatous type of healing was seen on *x*-ray examination. Her general condition was now good; her insulin requirements were lower and she was taking a diet of over 2,500 calories. In October she discharged herself and did not attend the diabetic clinic as arranged. She began to go downhill. A year went by, with readmissions and self-discharge against advice. The pneumoperitoneum was discontinued. She lost weight, but, as often happens in these cases of deterioration, her insulin requirements diminished and she died at home in 1952 at the age of 23.

This case shows all the worst aspects of the problem. A bad home environment, with dirt and squalor, and no moral standards. The patient did not speak the truth and her language was abusive. She had no intellect with which to reason. Diabetes began during adolescence; pregnancy occurred at the age of 19 and coincided with a primary tuberculous infection. Matters were made worse by puerperal sepsis, and in spite of a remarkable initial recovery the course was fatal owing to her lack of co-operation.

Another Side to the Picture

As a contrast there is the small group of private patients, of whom the majority are men. Many of these are Freemasons, and are business or professional men filling every moment of their lives. They are middle-aged and have heavy responsibilities. They are intelligent, have good homes and families, and have a high moral code. They are good patients and mostly keep in good health; but the

*Based on a paper read at a meeting of the East Midlands Branch of the Medical Women's Federation on October 31, 1954.

nuisance of their disease lies in its social restrictions. Most of them drive cars and have to be keenly aware of the danger of hypoglycaemia. Such functions as lodge dinners cause an emotional disturbance unrecognized at first. Later they can eat their meal with minor adjustments in diet and insulin, also in alcohol, so that it becomes no worry, but the pleasure it was intended to be.

Life insurance presents a problem. Some companies refuse to accept diabetics; those which are more enlightened impose a considerable loading. Superannuation varies. In the Civil Service, promotion to higher grades is barred, possibly unjustly. The fighting Services are, of course, rightly barred to diabetics. In the case of women, I support the view that nursing should not be chosen as a career but need not necessarily be abandoned if training is complete.

Personal and public hazards of employment are of considerable importance, and one such case may be cited in illustration.

Fred had been a railway employee for 25 years, and was a guard on a goods train, which involved coupling and uncoupling trucks. He had retained this job without mishap for the nine years he had been diabetic. He required a large amount of insulin, and, owing to a period of poor control due to middle-ear infection, was off duty until he was quite steady again. The authorities now became aware of the situation and felt that they could not agree to his continuing in his former employment, although it had suited him so well, because of the element of risk to himself and others. He was no scholar, and the only job which could be found for him was in the parcels office. This entailed heavy lifting and sweeping the platforms. Besides the loss in prestige to a man recently married late in life, there was a loss of 17s. 6d. a week in pay. To lose a pension and come out of the railway is hard advice to offer, and until some decision can be reached the emotional stress will affect his diabetic state.

The Problem as a Whole

It is estimated that 3 per 1,000 of the population of Great Britain suffer from diabetes, and it is believed that a similar number have minor or latent forms. Under stress or infection or with over-indulgence these may become frank cases, although from time to time one comes across patients who, having had a transient glycosuria many years before, have by their natural abstemious living kept their disease latent and are unaware that they are diabetic.

Improved therapy has increased the diabetic population, and in therapy one includes not only insulin but modern dieting and antibiotics. The young diabetic no longer is expected to die within twelve months, but lives fully. Although he may not reach old age, he works, plays, marries, and produces children with or without the inherited character. Elderly diabetics go on living with vascular changes that are probably no worse than those of other old people, and, indeed, the gangrene of their feet may have a better prognosis than has non-diabetic senile gangrene. This is the state of affairs which has been realized by the Ministry of Health (1953) in the circular on "Regional Planning of Diabetic Services." There is no doubt that on this account recognition of the problem has become more general, and hospitals and local authorities have taken stock of the situation.

Apologia

If one has the collector's instinct, diabetes makes a very good subject for a collection. There is much sorting and classification that can profitably be done. To have under observation large numbers of similar cases and to recognize what is dissimilar increases knowledge of a particular condition and its variations and allows one's judgment to develop in a broader way than if only the occasional case is seen among the general mass of patients. Six frank diabetics in a practice of 2,000 is all one would expect, and with such a small number there is no yardstick for measurement. If these, as they may do, run an easy straight course the assumption is that the management of diabetes is simple. On the other hand, they may be labile and complicated, swinging from hyperglycaemia to hypoglycaemia for no apparent reason. There is, of course, a reason, but it may be very difficult to find. If the doctor is too cautious or too casual the patient feels insecure and his diabetic control suffers.

We are dealing with a disease in which, because of its permanency, the doctor–patient relationship is most important. I suppose there is no disease in which the patient himself is expected to carry out more of his own treatment; and yet if he is to be well maintained there must always be a medical life-line strong enough to carry him through ketosis and coma at very short notice. I am therefore prepared to justify the setting up of special units in suitable centres where a trained team with proper facilities can advise and treat the patient and where the natural history of the disease may be studied. These two aspects should go hand in hand. I have stated elsewhere (Walker, 1953) what I consider to be the function of a clinic.

The Dietitian

Many of us are competent to advise and organize the plan of treatment, but many of us find that teaching a patient his diet is very tedious even when one is used to working out such a thing on paper. The patient usually has no basic knowledge, and our own is too specialized, so that this part of the work is very much better done by a trained dietitian than by a doctor. There are not enough dietitians to fill the vacant appointments on hospital establishments in Great Britain. The report of the Ministry of Health (1951) stated that there were then 440 members of the British Dietetic Association, from only three training schools. It was estimated that some 1,500 dietitians would be needed to staff the 2,600 hospitals and convalescent homes under the National Health Service. The position has not improved. There are very few dietitian catering officers. It is not possible to appoint enough therapy dietitians, and only a small number are capable of teaching. The U.S.A. do better than we do in this respect. On the other hand, the Scandinavian countries do not use dietitians at all: the medical and nursing staff take full responsibility. No attempt is made to cope with obesity, as the land flows too freely with milk, eggs, and butter.

The Health Visitor

I find that much of the dietetic teaching can be very well done by a specially trained health visitor. The health visitor has her S.R.N. and midwifery certificates; she then takes a course in sociology as applied to her work, which includes general nutrition and dietetics. Since 1950, in Leicester, the diabetic clinic has had the invaluable services of at first one and now two specialist health visitors seconded by the local authority. They are based on the clinic and see the patients there and in their own homes. They undertake the teaching of all new diabetic patients and follow up cases of special difficulty, such as the children, the blind, the old and bedridden, and the tuberculous. The health visitor has acted as liaison between the clinic, the general practitioner, the patient, and his school or work, and, through the almoner, for convalescence or national assistance when required. The secret of her success is that she is based on the clinic and knows the crucial problems in the management of the case, and the patient knows that she knows, so there are no doubts and no waste of time in getting treatment initiated. It is possible that prevention of delay in starting treatment prevents insulin resistance in some cases. It certainly reduces the number of admissions to hospital.

Children, unless they first come under observation in severe ketosis, are preferably treated at home from the beginning. One does not want a double set of values, and home treatment minimizes emotional disturbances of parent and child. The health visitor spends a little time at the

home talking to the mother to explain the essentials of adequate nutrition and carbohydrate equivalents. She can work out a regular routine and stress its importance, explaining the necessity for extra carbohydrate before games and swimming, also the advisability of giving sugar in cases of unexpected bad temper, as it may be associated with hypoglycaemia. She will visit the school and talk to the headmaster or headmistress, and also to the canteen supervisor, because it is often preferable for the child to have the school dinner with little or no modification.

In a similar way with adults, the health visitor calls at the home and sees his wife if, for example, the patient is a man who may be out at work. Unless the new patient is severely ill the initial stabilization is usually undertaken under working conditions. The health visitor has access to the personnel manager and canteen supervisor, and can often explain the situation so that a painter, say, can keep his job without climbing high ladders and scaffolding. Shift work can often be better sorted out by the health visitor on the spot. To come off shift work means a financial loss. Diabetes is no bar to hard labouring work provided it is regular and the diet adequate, but the change from sedentary clerical work to active gardening at the week-end may give rise to hypoglycaemia and require dietetic adjustments.

In a survey of the elderly diabetics in Leicestershire (1953), made in conjunction with the county health visitor, it was found that out of 113, 97 were living in their own homes, 12 were with relatives, and only 4 were in institutions. Roughly half (64) required insulin, and in only 16 of these was the district nurse administering it. In reviewing the complications, severe visual failure headed the list, and hypertensive cardiac failure, including coronary artery disease, came next. Severe peripheral vascular disease and diabetic neuropathy were significant in their relation to gangrene. As these patients get older and more infirm it is undesirable that they should be forced to attend the clinic, although many look forward to it as a social outing, but in certain cases the health visitor goes to the patient's home and makes her report to the patient's own doctor, merely keeping the clinic informed out of interest and giving follow-up details that are important. I know how much these visits help in the general management and hygiene of these elderly patients. Of 113 patients over 65 years old, 68 could bath themselves but 45 required help. The health visitor is delightfully persuasive about bathing. I am likely to offend if I probe too deeply. I now simply make a note—"More S and W"—and the health visitor sees that it is applied.

Convalescence and Rehabilitation

For the past few years the Leicester diabetic department has been blessed with the proximity of a convalescent hospital available for diabetics. Most convalescent homes will not admit diabetics, as they have a nuisance value: they require special food, and knowledgeable cooks are not easily found; they may also have hypoglycaemia, which is troublesome, and in certain homes there may not even be a trained night nurse capable of giving insulin. Burley-on-the-Hill is just an old and beautiful mansion set on a hill with a fine view and near a little market town. Here one may send difficult diabetics for a month, and they learn to live with their condition. The food is good, simple, and abundant, but correct in carbohydrate values, as it is supervised and served by the matron or her deputy. It is known when a patient cannot or will not help himself. Graded exercise is encouraged: at first, down the drive to the post office; then down to the town and a bus back; then both ways are walked. One notices the improvement in morale and the smartening in appearance. It is usual for the patients to leave at the end of their month, ready to return to work without delay; it may be, too, that the older ones return in better condition to their families, who have welcomed the rest from responsibility for a difficult member. Rehabilitation in diabetes is a special task that has not yet been fully tackled. It is quite distinct from passive convalescence.

The Diabetic Association

The British Diabetic Association is the first association of patients to be founded anywhere. In twenty-two years it has done much to help diabetics directly, both medically and socially, and an increasing amount of research is being undertaken through the scientific section. Branches are now being formed in the provinces, and at the inaugural meeting of the Leicester branch some 400 diabetics and interested persons attended. Only three of the twelve people on the platform were not diabetic, and I was told afterwards that it was the fact that these active and influential men stated that they were diabetic which had such a very fine effect on the other diabetic members of the audience. It was indeed a brotherly gesture.

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QUACKS IN FRANCE

[FROM A SPECIAL CORRESPONDENT]

France, with a population of about 43 million, has 38,000 practising doctors, but more than that number of so-called "healers." All the doctors, from the venerable *grands Patrons* to the young men and women who are starting on their careers, have strong feeling about these healers. Professional tradition has restricted collective comment, but now the doctors are expressing themselves vigorously and unitedly about recent developments of a flourishing racket.

A statement on the healers was recently made by the Seine county's section of the national Ordre des Médecins. The Seine county embraces Paris and its thick belt of suburbs, and has 9,300 doctors. President of their section of the Ordre des Médecins is Dr. Jacques Richier, a well-known ear, nose, and throat specialist.

Most of the healers in France, according to Dr. Richier, do their business round the large towns, and 75% of them make big money. At the home of one of them who was arrested for the illegal practice of medicine, gold ingots worth £12,000 were found. They had been bought, said the healer, with the proceeds of his last three months' work.

There are village healers to whose consulting-rooms regular motor-coach services run. One old man claims to have treated a million people. Thousands have stayed in his village for a few days, and have visited the "magical man" three times, paying 10s. a time. Refreshment rooms have been built for clients. Some of the sick people are accompanied by healthy members of their families who pay the healer for preventive treatment.

Though there are more healers than doctors in France, there are fewer now than there were eight years ago, and their number is still slowly decreasing. A Government decree of September 25, 1945, on the illegal practice of medicine, empowers the Ordre des Médecins to report offenders to magistrates' courts. This power is being exercised with increasing vigour. Last year the Ordre des Médecins for Paris and its suburbs was directly responsible for the prosecution of 88 healers. Fines ranging from £8 to £50 were imposed, and in some cases payment of damages, ranging from £10 to £30, was ordered. These damages are paid into a fund which assists aged, needy doctors.

The healers ask for an official statute, which would give them official recognition. "If they got this," says M. Georges Duhamel, a noted doctor and writer who is a member of the French Academy, it would be "a diploma of trickery."

Successful Anti-doctors

The big-business healers—those whose reputations grow as they are cited in one legal case after another, and to whom patients travel in special motor-coaches—are roughly

in three types: pseudo-doctors, anti-doctors, and mystics. The macabre results obtained by the shamefully named "Witnesses of Christ" caused a recent revulsion against the mystics. The Seine doctors say about this sect: "Denying the malady as well as the pain, they make their followers forget their ills. But they cannot deny death." The pseudo-doctors are caricatures of the *grands Patrons* of medicine. Garbed in white, they receive their patients in sumptuously equipped offices, where they submit them to various tests, sometimes using gadgets, of which the pendulum, "manipulated with a sure hand," is typical. They end with a cabalistic prescription based on common or inactive substances, which are named in court cases. They do excellent business. But the anti-doctors are even more successful. All their behaviour is calculated to remove apprehension or respect. Working in a room behind a café, with their shirt-sleeves rolled up, they grip their patients by the shoulders, talk familiarly with them, roughly massage them or finger them, and prescribe crude "magnetized" poultices. They work "with the quiet consciences of those who never ask themselves questions."

The Seine doctors say that comparatively few people consult the healers on their own initiative. They go because they have heard of "marvellous" cures. Doubters, some strong-willed, join the throng. Pendulum-swingers, mesmerists, clairvoyants, bone-setters, big quacks and little messiahs—all are doing well. Many healers have been charged with illegally practising medicine. If found guilty they are fined. Doctors, and many other people, say they should be imprisoned.

MIGRAINE AND VASCULAR ALLERGY

INTERNATIONAL SYMPOSIUM IN BASLE

[FROM A SPECIAL CORRESPONDENT]

The second meeting of the International College of Allergists under the presidency of Dr. DAVID HARLEY (London) was held in the Blue House, Basle, from July 3 to 8 on the subjects of migraine and vascular allergy. The proceedings began with an account by A. STOLL and E. ROTHLIN, both of Zurich, of the isolation and identification of the various alkaloids of ergot and the discovery that ergotamine relieves the headache of migraine. It is of interest, in passing, to note that Rothlin's discovery of the effect of ergotamine on migraine was based, as have been so many similar discoveries, on a bogus hypothesis: in this instance that headache is due to overaction of the cervical sympathetic nerves. The remainder of the first part of the meeting was concerned with the nature of the disturbances occurring in migraine, the factors precipitating attacks, and its treatment.

Vascular Sequence in Migraine

G. W. PICKERING (London) discussed the general principles concerned in somatic and visceral pain, and the experimental methods available for the study of headache.

H. G. WOLFF (New York) distinguished three phases in the migraine attack—the vasoconstrictor, the vasodilator, and the oedematous. The aura, often a scotoma, is attributed by Wolff to vasoconstriction of the retina or calcarine cortex. He stated that vasoconstriction can be seen and photographed in the retina, that during this phase the vessels of the bulbar conjunctiva are narrowed and abnormally sensitive to noradrenaline applied locally, and that the scotoma can be relieved temporarily by vasodilator drugs such as amyl nitrite. In a later paper P. VALLERY-RADOT (Paris) also said that the scotoma can be abolished by amyl nitrite, benzyl benzoate, or subcutaneous injection of acetylcholine. H. KRAYENBÜHL (Zurich) had, on the other hand, seen vasoconstriction in the retina opposite to the side of the headache. The second phase (of dilatation), said Wolff, was manifested by headache chiefly due to expansion of the temporal and other arteries of the scalp, and ergotamine relieved the headache because it narrowed these arteries. Studies of water and electrolyte balance had shown that immediately preceding the headache there is retention of water, sodium, and potassium, attributed in part to renal vasoconstriction, on the basis of the finding that there is a reduced renal output of creatinine. With the onset of headache there was a diuresis of water, sodium, and potassium. These generalized changes in fluid balance seemed to have nothing to do with headache, since if they were prevented by acetazoleamide ("diamox") the headaches occurred just the same. What seemed of greater importance was local oedema of the temporal arteries (observed in biopsy specimens) and of the surrounding tissues during the attack. Apparently this oedema fluid contained a substance of molecular weight about 200, which on injection into the skin elsewhere produced pain.

W. BÄRTSCHI-ROCHAIX (Berne) discussed the electroencephalographic findings—bursts of slow waves suggestive of activity of a subcortical focus in the prodromal phase, and a tendency to asymmetry of the α waves between the attacks. T. DALSGAARD-NIELSEN (Copenhagen) had found moderate dysrhythmia during attacks which he was unable to induce with ergotamine. Discussion brought out the very bizarre nature of the events in migraine: a phase of vasoconstriction thought to involve fundus, conjunctiva, and cerebral cortex on one side, followed by vasodilatation, oedema, and the release of a pain-producing substance. So far as is known this can happen in the absence of the sympathetic nerves. As regards inheritance, opinions differed on whether migraine conforms to a recessive or a dominant pattern.

Prevention and Treatment of Migraine

Induction of attacks was discussed by P. KALLÓS (Hälsingborg) and DALSGAARD-NIELSEN. The former had studied 15 patients who had both migraine and hay fever or asthma; inhalation of the antigen produced headache and hay fever or asthma; the headache could be prevented by ergotamine, the other two conditions by antihistamines or adrenaline. Unfortunately the antigen would not produce the aura that commonly precedes the migrainous attack. The latter had found that the dose of nitroglycerin needed to produce headache between the attacks was lower in migrainous than in normal subjects. He drew attention to the occurrence of morning headache between and before the characteristic paroxysms.

VALLERY-RADOT reviewed the treatment of migraine. During the phase of headache, he said, ergotamine tartrate, by subcutaneous or intramuscular injection, was the most efficacious agent. Ergotamine tartrate (1 mg.) could also be given by mouth in combination with caffeine (100 mg.), or, if vomiting were troublesome, as a rectal suppository of 2 mg. ergotamine and 100 mg. caffeine. During the oedematous phase analgesics had a comparatively feeble effect. KRAYENBÜHL thought that to prevent attacks dihydroergotamine was the most efficacious drug in patients showing vasomotor instability, while in attacks possibly related to epilepsy a combination of mesantoin and caffeine was best. STOLL pointed out the importance of the doctor–patient relationship, and it was agreed that a controlled therapeutic trial would be desirable to assess the relative efficacy of different drugs in preventing migraine.

Mechanism of Inflammation

The next group of papers were those dealing with the mechanism of inflammation. W. FELDBERG (London) gave a comprehensive review of chemical mediators in the inflammatory response. Histamine, he said, would account only for vasodilatation, increased permeability, and itching, but not for adhesiveness of the platelets, cellular infiltration, or pain. Hyaluronidase might be concerned in the early stages of the inflammatory response. The spread of dyes and carbon particles suggested that one of the earliest changes

in the neighbourhood of trauma was a change in the constitution of the intercellular substance from gel to sol; the hyaluronidase content of burned tissue was increased. The third group of substances concerned were polypeptides. Stimulation of the nerve to the salivary glands liberated acetylcholine, which stimulates secretion and had been shown by Hilton and Lewis to release an intracellular enzyme which appears in the saliva and in the tissue spaces, where it splits proteins into polypeptides resembling bradykinin. The depressor action of saliva was due to an enzyme which splits protein. A polypeptide, possibly bradykinin, was also released by diluting serum and by the contact of plasma with glass or metal. Bradykinin might be the pain-producing substance. Other polypeptides possibly concerned were Menkin's factors leucotaxin and exudin, the action of the former being suppressed by cortisone and corticotrophin, the latter by corticotrophin only. Finally, said Feldberg, Miles and Schachter had found that when guinea-pig plasma is diluted 1 in 400 and left for an hour an α globulin is found which increases vascular permeability and appears to be a protease, since it is inhibited by the trypsin inhibitor found in soya bean.

New Test for Allergens

One of the most striking presentations at the meeting was that of H. STORCK, R. HOIGNÉ, and W. GROSSMAN (Zurich) on a new serological method for identifying allergens. They had shown previously that an allergen added to a sensitized serum would cause conglomeration of platelets. They now showed, using a sensitive nephelometer, that adding an allergen to a sensitized serum causes turbidity at certain dilutions of the allergen. They also demonstrated that the capacity of serum so to react with the allergen is due to the presence in it of two factors, a specific factor which reacts only with the allergen and which dialyses through "cellophane," and a non-dialysable non-specific factor which is present in the serum of guinea-pigs, cows, and horses, but absent from that of rats and rabbits.

Vascular aspects of allergy were discussed by J. WALDENSTRÖM (Malmö), who drew attention to the possible relationship between polyarteritis nodosa and the use of drugs like sulphonamides. Transitional forms between polyarteritis, temporal arteritis, and pulmonary arteritis occurred. Cortisone or corticotrophin might produce a dramatic and persistent cure.

Loeffler's Syndrome and Ascariasis

W. LOEFFLER (Zurich) described transient eosinophilic lung infiltration. This condition was characterized, he said, by a transient pyrexia lasting a few days to a few weeks, transient infiltration of the lung, resembling pulmonary tuberculosis, pneumonia, or even miliary tuberculosis, appearing on the third and disappearing on the fourteenth day, and an eosinophilia varying from 5 to 66%. All ages were affected and there was a striking seasonal incidence, with the peak in July and August. This strongly suggested a parasitic cause, and ascaris infection was by far the most likely, for the following reasons: a similar illness with lung infiltration, fever, and eosinophilia could be produced in guinea-pigs by feeding ascaris eggs; an outbreak in troops had pointed strongly to an alimentary cause; and in two human volunteers ingestion of ascaris eggs had reproduced the syndrome. However, ascarides had not been found in the sputum of affected patients, and only 25% excrete ascaris eggs in their faeces. Loeffler was clear that the syndrome he described was not related to polyarteritis nodosa, of which he had seen only one case.

The meeting was terminated by a beautiful film, shown by J. LECOMTE (Liége), of the circulation in the mesoappendix in the rabbit. Irrigation with a weak solution of a protein to which the rabbit had been sensitized produced vasodilatation, and adhesion of leucocytes to the vessel walls and their agglutination into plugs. Histamine produced only vasodilatation. Antihistamines did not, but cortisone did, inhibit the leucocyte aggregation.

Correspondence

ABO Blood Groups and Hypertension

SIR,—The excellent paper by Drs. R. D. H. Maxwell and Katharine N. Maxwell (*Journal*, July 16, p. 179) on blood groups and hypertension is very welcome; it puts on record on the basis of a large and carefully collected sample data on blood-group frequencies in relation to yet another disease.

With one possible exception the results are negative. The exception is a deficiency of AB's, which in fact appears only in the men. The authors are rightly cautious and conclude that on the evidence available the association is unproved and probably due to the accidents of sampling. Nevertheless the evidence is perhaps rather stronger than they suggest.

Their results are as follows:

Blood Group	Control	Hypertension	
		Males	Females
O	3,853	309	829
A	2,485	209	513
B	817	72	165
AB	263	7	43
Total	7,418	597	1,550

Comparing AB's against the other three groups combined, the difference between the hypertensive men and the controls gives a χ^2 for one degree of freedom (with Yates's correction) of 8.84, corresponding to a probability of 1 in 340. A similar comparison of women and controls gives a non-significant χ^2 of 2.09. There is also some direct evidence of a difference between hypertensive men and hypertensive women in the proportion of AB's, χ^2 being 4.18. On the other hand, it must be remembered that one comparison has been arbitrarily selected, after inspection of the data, from a number that could have been made. Furthermore, the controls show a rather higher proportion of AB's than is usually found.

Fisher's test for unreasonableness of group proportions[1] provides some further evidence. In the hypertensive men, on the basis of the observed numbers in groups O, A, and B, the expected number of AB's is 20.111 as against the 7 observed, χ^2 being 6.22 for one degree of freedom. Hence, quite apart from any question of a comparison with controls, the men show a suspicious deficiency in the number falling into group AB. In contrast, in the women the expected and observed numbers are almost identical, 42.897 and 43 respectively. The control series, however, is also rather peculiar, showing an excess of AB's instead of the deficiency which is more usual with large samples. The expected number is 219.760 against the 263 observed, χ^2 being 6.28.

There is one further point. The authors consider that the deficiency of AB's, if real, would suggest an advantage in belonging to group AB. It seems equally probable, or more probable, that such a difference would indicate a disadvantage, hypertensive men of group AB tending to die younger and so not to appear in the series.

While agreeing with Drs. R. D. H. and K. N. Maxwell that on the results described the only safe conclusion is that a real deficiency of AB's is unproved, it does seem that the evidence is sufficiently suggestive to make it well worth while investigating a further series. It is much to be hoped that they or other workers will be able to provide further data, concentrating especially on men and keeping a careful watch for any associations with age.—We are, etc.,

IAN AIRD.
H. H. BENTALL.
J. A. FRASER ROBERTS.

London.

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Treatment of Barbiturate Poisoning

SIR,—I wish to draw attention to a few points raised by Dr. T. J. Thomson and Professor Stanley Alstead (*Journal*, April 23, p. 1022), in the treatment of the patient suffering from barbiturate poisoning, which are contrary to the suggestions of other writers, particularly those of the Scandinavian school.

The first is the authors' insistence that "no matter what the outcome of treatment with emetics the stomach must be washed out" and their suggestion that about one gallon (4.5 litres) of tepid water is needed for this purpose. Møller,[1] supporting the prior observations of Harstad,[2] studied the value of this procedure in 100 serious cases (23% death rate) and, using 10 litres of fluid in the first few hours after the ingestion of the barbiturate, he found that in 62% of patients less than 10 mg. of barbiturate was recovered by lavage and less than 100 mg. was removed in 85% of these patients by this treatment. He further stated that persons contemplating suicide rarely ate before taking the barbiturate and washed the drug down with plenty of water, so that there was a quick passage of the barbiturate into the intestine usually before the patient was discovered and given treatment. Further, following the administration of 10 litres of a dilute solution of barium sulphate under *x*-ray control, he found that he could only recover 7 litres even after a few minutes, the remaining 3 litres passing into the intestine. Møller consequently condemned gastric lavage on the following grounds: (1) The patients were usually brought in for treatment after the drug had entered the intestine, and gastric lavage yielded a poor return of barbiturate from the stomach. (2) The water used for gastric lavage increased the dangers to the patient by helping to convey the barbiturate further down the intestine, thereby accelerating its solution and rate of absorption. He further disagreed with the administration of aperients and pointed out that, as the intestine soon became atonic, these would only serve as a source of irritation.

Our own results[3] support Møller's claims, and I am a strong advocate of his suggestion that gastric lavage should be abolished and gastric aspiration undertaken, after preliminary endotracheal intubation in the absence of pharyngeal reflexes, provided treatment is commenced within 4–5 hours of ingesting the barbiturate.

Møller, supporting Nilsson,[4] also states that respiratory paralysis is rarely the basic cause of death in a patient suffering from prolonged barbiturate poisoning, but that the prime cause of death is circulatory failure of both central and peripheral origin. This is in agreement with our own findings and is supported by the elegant work of Kirkegaard[5] on rats poisoned with "aprobarbital" (allyl isopropyl barbituric acid). Møller differentiates acute barbiturate poisoning from morphine poisoning in that, whereas circulatory failure is the prime cause of death in the former and there is, at least in the early stages of the condition, an adequate respiratory function, respiratory failure is the prime cause of death in the latter, and here there is an adequate circulation provided that the oxygen tension of the blood can be maintained.

There is also disagreement regarding the value of sodium bicarbonate in the treatment of barbiturate poisoning. Although I agree that it is wrong to administer sodium bicarbonate in the early stages of the intoxication, its subsequent use seems most reasonable. Nilsson[4] and Fischer and Salzer[6] advocate the liberal administration of sodium bicarbonate to convert the barbituric acid into its ionized sodium salt and so effect its readier solution into the blood. This would facilitate its elimination by the kidney or detoxification by the liver. Nilsson pointed out that up to 20% more barbiturate may be excreted in the presence of a mild alkalosis. These clinical observations support those of Salzer and Fischer,[7] who increased the rate of veronal excretion in rabbits given this barbiturate. They administered intravenous sodium bicarbonate, which raised the urinary *p*H from 4.5 to 7–8, and stated that with this procedure the toxicity was also appropriately modified.

The greatest point of contention arises regarding the value of the central analeptics in current use—that is, picrotoxin, leptazol, nikethamide, amphetamine, and "geastimol"—in the treatment of barbiturate poisoning, and the work of Nilsson,[4] Clemmesen,[8] Locket and Angus,[9] and others argues strongly against their use. Their excellent results (mortality rates 1.6–4%), using only a thorough routine of medical management, afford strong support for their argument, and it is interesting to observe that their patients have recovered from prolonged barbiturate coma of up to ten days' duration on this regimen, and that barbiturate was detected in their urine for an even longer period. These authors stress that central analeptics should never be used except possibly as a temporary expedient to buffer a depressed respiration which is causing grave concern. The suggested routine under these conditions is the intramuscular administration of amphetamine sulphate (25 mg.). A more effective and safer respiratory stimulant under these conditions is 2:4-diamino-5-phenylthiazole hydrochloride (D.A.P.T. or "daptazole"),[3] which in therapeutic doses appears to be almost completely devoid of any toxic side-effects. This substance may be given by the intramuscular or intravenous route in doses of 10 mg. at 5-minute intervals until satisfactory ventilation is restored. It seems to be particularly useful as a buffer to respiration where pneumonia complicates a case of barbiturate intoxication.

The physician treating a case of barbiturate poisoning is swung on the pendulum of medical treatment between the extremes of conservative management, with its inherent risk of lethal complications such as pneumonia, severe circulatory failure, etc., following prolonged coma, and the use of central analeptics, which in excessive doses (for which there is still an inadequate individual index) are thought to kill by producing an irreversible secondary anoxic depression of an already impaired cortical metabolism and mechanism.[10 11] Our own treatment provides a compromise between these two extremes.—I am, etc.,

Melbourne. A. SHULMAN.

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The Ban on Heroin

SIR,—There have been many letters appealing against the ban on the manufacture of heroin, but I have not seen a single article giving the other side of the picture. I am by no means pro-Government, whether it be Conservative or Labour, but I have had to deal recently with a heroin drug addict, and I have learnt a thing or two that I did not realize before and which I imagine quite a number of others may not know.

Though there may be comparatively few persons registered as addicts in England and Wales, etc., there are a large number of unregistered addicts who buy their heroin at exorbitant prices from the registered. They may be known to the police, but they cannot be stopped in this illegal traffic unless there is evidence of sale or the actual purchase is witnessed.

Besides the really degrading effects of addiction, there is also the method of administration which is adopted by many of these unfortunates, who are usually also addicts to other drugs at the same time. These persons give themselves intravenous injections of heroin by means of a fountain pen filler, a piece of paper, and a hypodermic needle. The drug is previously placed in the glass filler and those practised persons make an air-tight juncture with the needle by means of a piece of paper. The needle is then inserted into a vein in the arm and the heroin is dissolved and injected by alternately sucking the blood into the apparatus

and injecting into the vein. This may be repeated two or three times till all the powder is injected; as the apparatus is very rarely cleaned and never sterilized and often passed from one person to another, one can imagine what risks of infection and disease are present to these misguided people. This apparatus has the advantage also of easily being concealed and easily being assembled.—I am, etc.,

Birmingham, 32. G. H. BOSTON.

Hypodermic Injection Technique

SIR,—I should like to comment on the letter from Dr. L. P. Lockhart (*Journal*, February 12, p. 415) on hypodermic injection technique stressing the importance of withdrawing the plunger to ensure that a vein has not been entered, as I recently heard that it is still current teaching in medical schools apparently without its limited applicability being mentioned.

Withdrawing the plunger remains necessary when an intramuscular injection of a drug which must not enter a blood vessel is being given. It also remains desirable before subcutaneous injection of such material to single individuals. In both these circumstances, however, it entails using a syringe which has been sterilized before each such injection.

The procedure is not applicable when a mass inoculation method, involving the sterilization of the needle only between injections of different persons, such as that described by Fleming and Ogilvie,[1] is in use. This must be so, since the object of such methods is to avoid the syringe becoming contaminated with reflux fluid from a potentially infected subject. Evans and Spooner[2] and Hughes[3 4] have shown that mere removal of the needle from the syringe after an injection may lead to such contamination, and Hughes found evidence of the presence of body fluids in needles following both intramuscular and subcutaneous injections. This was confirmed for subcutaneous injections by Fleming and Ogilvie. With the mass inoculation methods now advocated, though, such contamination will not pass beyond the needle while this is still in place on the syringe, and hence can be rendered harmless by sterilizing the needle without (or before) removing it. An attempt, as suggested by Dr. Lockhart, to withdraw the plunger after introducing the needle, however, would, as has been pointed out by Hughes, be liable to cause the aspiration of possibly infective body fluids into the syringe (calling for complete sterilization of the latter) even when the needle had not entered a vein.

Most prophylactic inoculations, however, are, or may be, given subcutaneously. Though the antigens used should certainly not be injected into a blood vessel, certain precautions, not applicable to the intramuscular route, can therefore be taken which should prevent their entry in significant volume direct into the circulation, without withdrawing the plunger for this purpose. The following are suggested: (*a*) After introducing the needle under the skin for about two-thirds of its length the point may be turned through a right angle or more but without advancing it further. If this can be done without resistance the point can hardly be in the lumen of any large vessel and will presumably break out of a small one. A fresh vessel should not be entered if the needle is not advanced but merely turned. (*b*) Instead of the common practice of rendering the skin taut before making the injection, the needle may be introduced near the base of a pinched-up fold of skin, but above the level of the skin on each side of this fold, and parallel with the main surface rather than at a downward angle to it. It seems unlikely that any vein will be so pinched up in the fold as to be entered by a needle, though it should be recalled that Hughes, after injecting into such a fold of abdominal skin, noticed appreciable skin bleeding on withdrawing the needle on four of the five occasions when erythrocytes were found in the needle. This would suggest, at least, some damage to a small vessel. (*c*) After introducing the needle the tip may be raised so as to be felt under the skin by a finger of the free hand. This finger may be held over the needle point while the injection is being made. If this is done relatively slowly the local swelling produced should generally be palpable. When a lump does not start to form almost at once the possibility that a vessel has been entered may thus be suspected in good time.

In all cases, of course, the normal situation of the large superficial veins must be avoided when making a subcutaneous injection. The site of election is probably the area at the level of, but behind, the insertion of the deltoid.—I am, etc.,

London, S.W.1. G. T. L. ARCHER.

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Bacteriological Environment of Newborn

SIR,—Drs. P. N. Edmunds, T. F. Elias-Jones, John O. Forfar, and Charles L. Balf have shown in their careful and thorough investigation, "Pathogenic Staphylococci in the Environment of the Newborn Infant" (*Journal*, April 23, p. 990), that there was a high carrier rate amongst the nurses attending domiciliary confinements. In spite of this the staphylococcal carrier rate of the babies born at home remained low. Forfar *et al.* show clearly: (1) the staphylococcal carrier rate of nurses attending mothers and babies in hospital and at home is, for all practical purposes, equal. (2) The carrier rate in infants rose after eight days to 40% in hospital. (3) The equivalent figure for babies born at home was 8.6%. (4) Mothers in hospital do not transfer to their babies the maternal staphylococcal organisms.

The conclusions to be drawn from these points are these (which seem to have also received scant consideration in your leading article (*Journal*, July 9, p. 111)): Reduce the exposure to nurses of the babies born in hospital, and the incidence of staphylococcal infection will drop. In domiciliary maternity work, the nurses come into contact with the baby for about three-quarters of an hour daily during the first three days; thereafter for about 20 minutes daily. In hospital the time a baby is handled by nurses during the 24 hours is very much greater, and he is usually exposed to three different nurses per day. The staphylococcal bombardment to which the baby is thus exposed in hospital is infinitely greater than the domiciliary baby–nurse contact would allow, not only in quantity, but also in quality. However perfect the nursing technique is, with the much greater exposure time for the nurse contact in hospital, the chances of staphylococcal infection are at least geometrically greater than during domiciliary maternity nursing.

Finally, to put all this into practice, reorganize the hospital maternity wards into small cubicles or adequately screened areas where both mother and baby are housed, and where mother can take over many of the nursing duties as early as the second or third day, except in the exceptional circumstances. Only in this way will you achieve the low figure as reported by Forfar *et al.* for domiciliary maternity work in the maternity hospitals.—I am, etc.,

Edinburgh. E. V. KUENSSBERG.

Acute Food-poisoning

SIR,—Few practitioners see so much of acute food-poisoning as do the surgeons on big ships on long voyages through the Tropics. One experience last year was 260 cases of Sonne infection, homeward bound from Australia, beginning 36 hours after leaving Bombay, confirmed by examination of four separate stools sent ashore at Aden.

I hope, therefore, that Dr. C. Hardwick (*Journal*, May 14, p. 1205) will not be offended if it is suggested that his scheme of treatment, as far as drugs are concerned, is inadequate. This is mine: (1) If seen in the early vomiting stage, give sodium bicarbonate drinks freely, until the stomach is emptied. (2) Then give castor oil, 1 oz. (28 ml.). Those who allege that they are unable to take castor oil take longer to clear up. (3) One hour after the castor oil, give mist. kaolin. c. morph. ½ oz. (14.5 ml.) two-hourly, or even more. (4) In some cases, both of staphylococcal and Sonne

infection, pain and shock at onset are nearly as severe as in perforated peptic ulcer. These should be given morphine, ⅓ to ½ gr. (22 to 32 mg.). Few cases treated thus will require more specific treatment, intravenous therapy, etc. About once a year at sea I get an attack myself; and that is how I treat it. Also, I take a bottle of brandy to bed with me. I regret that I cannot prescribe that for all my patients.—I am, etc.,

Bristol, 8. GEORGE L. ALEXANDER.

Aspirin and Ulcer

SIR,—Drs. A. Muir and I. A. Cossar's paper on "Aspirin and Ulcer" (*Journal*, July 2, p. 7) lacks any statement that the victims of gastric ulceration, made worse for the purposes of the paper, offered themselves freely for experiment. The conversion, for example, by aspirin of a previously consistently negative test for faecal occult blood to a strongly positive one does not, at first sight, come under the heading of medical therapeutics. In the case of the patient treated with aspirin before operation, was the surgeon's approval in addition obtained? Acute erosive gastritis is an unusual objective in premedication.—I am, etc.,

London, S.W.1. R. J. V. PULVERTAFT.

*** Professor Pulvertaft's letter was shown to the authors of the article on "Aspirin and Ulcer," and their reply is printed below.—ED., *B.M.J.*

SIR,—Professor Pulvertaft's criticism of our paper (*Journal*, July 2, p. 7) hardly faces the facts. Vast quantities of aspirin are swallowed annually without medical control. Many doctors prescribe aspirin irrespective of the patient's gastric condition. We have frequently seen aspirin given in medical units to patients with haematemesis for incidental minor painful conditions. All this is regarded as a safe routine. All we have done is to follow it with our eyes open.

Surely there is all the difference in the world between experimentation with drugs of doubtful toxicity and observing the effects of one which is prescribed with impunity as perfectly safe, with the admitted object of showing that it is not. The patients knew that they were taking aspirins for experimental purposes. Mr. Brandon, the surgeon, also knew. "The victims of gastric ulceration made worse for the purposes of the experiment" were all being prepared for gastrectomy, and positive faecal occult blood tests were, on them, of little moment.

Finally, the procedures we carried out were thought to combine the least discomfort to the patient with the maximum of definite information. It is hard to contemplate a negative answer to the question: "May I give you two aspirins and study their effect on you?"—We are, etc.,

A. MUIR.
Carluke, Lanarkshire. I. A. COSSAR.

Fluorine Hazards

SIR,—When Roholm in 1937[1] published his classic monograph on fluorosis it attracted but little attention in Britain, although serious consideration could have predicted the fluorine hazards here which have since been recorded.[2,3] The recent description at the B.M.A. Meeting of 48 cases (14 so far fatal) of "bauxite-fume pneumoconiosis" in Canada (*Journal*, July 9, p. 135) suggests that dangers associated with the industrial use of bauxite are not limited to any one part of the world; there remains also the possibility of neighbourhood hazards outside a factory.

In this country the adverse effects on animals of fluorine from atmospheric pollution by fluorine compounds, known to be naturally present in certain iron ores and marine clays and coals or added as flux in numerous processes of manufacture, have become a matter of urgency to farmers; and an answer to questions in Parliament (see *Journal*, July 9, p. 147) has assured members of their National Union that the inquiry being carried out round Stoke-on-Trent by the Ministry of Agriculture, Fisheries, and Food has been extended to other parts of the country.

While we appreciate the care being shown for lower animals, we regret that man is the subject of so much less solicitude. The Beaver Report[4] noted that power stations and similar coal-burning installations are not under control, and the Chief Alkali Inspector[5] has pointed out the extreme difficulty of controlling fluorine emissions from the aluminium, clay, and steel industries; but the Ministry of Housing and Local Government has decided in favour of extending clay working in Buckinghamshire against the wishes of the county council,[6] while, in spite of local opposition, the Ministry of Health continues to add fluorine to the drinking-water in four areas of this country (*Journal*, January 29, p. 284, and March 26, p. 789).

We consider that at the present time the amount of fluorine ingested in this country by man deserves at least as serious consideration by our profession as that given to the problem in cattle by the National Farmers' Union.—We are, etc.,

DAGMAR C. WILSON.
Oxford. H. M. SINCLAIR.

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2 Murray, M. M., and Wilson, D. C., *Lancet*, 1946, 2, 821.
3 Medical Research Council, Memorandum No. 22, 1949.
4 *Report of the Committee on Air Pollution*, 1954. H.M.S.O., London.
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6 *The Times*, May 13, 1955.

Simultaneous Ingestion of Poison and Antidote

SIR,—A child of 2 was brought to me at 5.15 p.m. He had gone into the house next door, found it empty, and began to eat the tablets prescribed for the (adult) neighbour. A tablet was produced which was obviously dexamphetamine, and another which could not be identified. But as the neighbour said she was having these "for her nerves" it was presumed to be some sedative. There seemed to be no ill effects in the hour which had elapsed since the tablets were taken. I saw the child again two hours later and again he seemed quite well. The only thing was that it was after his usual bedtime and he did not seem sleepy. I was told that 13 tablets in all had been taken but not how many of each kind. So I deduced that he had taken a relative excess of dexamphetamine and prophesied little sleep that night. He slept three hours only. I found out from the neighbour's doctor that the other tablets were chlorpromazine. There were no ill effects and no treatment was given at any time.

I have dealt with cases of poisoning before, but this is the first time I have known (presumably) poisonous doses to be taken together with an antidote.—I am, etc.,

Leeds. W. STANLEY SYKES.

Book Reviews

SIR,—Few British authors would fail to endorse Sir Heneage Ogilvie's remarks (*Journal*, July 2, p. 58). A certain capacity for tolerating adverse criticism is, of course, part of a general education, and no one should embark upon authorship unless prepared for it. Favourable reviews are gratifying as evidence of a hard task well done and well received. However, it seems preferable in these days of abundant authorship that the suggestion put forward by Sir Heneage Ogilvie should be adopted by the *British Medical Journal*.

A further reason for anonymity is suggested by your reviewer's appraisal of Professor F. J. Browne's well-known book, *Antenatal and Postnatal Care* (*Journal*, July 16, p. 185). I recently encountered another, unsigned, review of this book in another professional journal. A comparison will emphasize the wide divergence of opinion existing between two competent and highly experienced reviewers. Your reviewer states that this book is a classic and requires not even commendation. The other states that it has many faults, has a misleading title, and contains many instances of a "lack of proportion and balance," whereas your reviewer, recognizing the obvious difficulties, believes that

most have been overcome, and his final judgment, wherein he states that "the surmounting of most of these difficulties is merely one example of the skill which has gone to the making of a book which will long continue to hold a place in the first line of the world obstetrical literature," is in curious contrast to that of the unknown reviewer. The latter concludes his remarks by saying: "It will thus be seen that much alteration of this book is necessary before it can be confidently recommended to the undergraduate or doctor."

We may well be approaching a time when "nobody is anybody" who has not written a book. It therefore behoves us clearly to define the purpose of a book review. Surely it is to outline briefly, concisely, intelligently, and fairly what an author has attempted to accomplish, and the ultimate success or failure of the book must be left to time and the discriminating reader. The widely differing opinions expressed by your reviewer and by the unknown one I have mentioned further emphasize the view expressed by so experienced an editor as Sir Heneage Ogilvie, that reviews should be unsigned.—I am, etc.,

Liverpool, 1. H. VINCENT CORBETT.

Clinic for Alcoholics

SIR,—I have been requested by the council of the Society for the Study of Addiction to ask you to be so good as to publish this letter to correct any false impressions that may have arisen from articles in the lay press and from a statement in the *British Medical Journal* of June 25 (p. 1542), that the Society, together with the Church of England Temperance Society and the National Association for Mental Health, is responsible for the conduct of a clinic for the treatment of alcoholism at 14, Gloucester Place, London, W.1.

While the council has every sympathy with the object of the clinic and with its members participating in the work in their private capacity, I am asked by the council to emphasize that the Society has played no part in the founding or running of the clinic. As to how far the Society is prepared to be identified with the clinic at a later date must depend on discussion by the council. Such discussion may well involve legal questions relating to the Society's constitution.—I am, etc.,

London, W.4. W. R. BETT,
President, Society for the Study of Addiction.

Gonorrhoea Statistics

SIR,—There are, of course, other factors than those enumerated by Drs. G. H. Knight and W. Fowler (*Journal*, July 16, p. 203) which influence the rise and fall of incidence of venereal infections. Their statement is an over-simplification of what is really a very complicated matter. We believe that the investigation undertaken by the British Co-operative Clinical Group may give useful results; Drs. Knight and Fowler are quite sure that it will not. At this stage a decision between us will only be possible when the results of the investigation are known. If our critics feel that it is a waste of time they are entitled to withhold their support.

The Co-operative Clinical Group is not limited to any one line of investigation and the committee of that organization will be glad to consider practical suggestions, especially if they are submitted in detail. This could have been done without seeking the hospitality of your correspondence columns.

The suggestion that the Medical Society for the Study of Venereal Disease has no regard for the needs of its members who live in the provinces can be rejected out of hand. Nearly all venereologists conduct some evening sessions and it is always difficult to find times at which all may be free to attend meetings. In general, the claim has lain between Friday evenings and Saturday afternoons, and the question of the time preferred by members has been put repeatedly at general meetings and, in 1952, by postal ballot. In every instance there has been an overwhelming vote in favour of Friday evenings, although the majority of members of the Society live in the provinces. Members who live much further afield than Birmingham do attend these meetings regularly; some of them even come from Edinburgh. Notwithstanding the wishes of the considerable majority, the council of the society has tried to meet the needs of the minority by holding two recent meetings on Saturday afternoons, one on November 27, 1954, and the other on March 26, 1955. There was no increase in attendance of members from the provinces, and I believe that no representative from Birmingham attended on either occasion. The council has gone further and a little while ago invited members of the Society in the Birmingham area to organize a general meeting in that city in March, 1956. This invitation has been accepted, and I hope that on that occasion Drs. Knight and Fowler, while maintaining a spirit of healthy criticism, will also turn their energies to co-operation and support.—I am, etc.,

London, E.1. A. J. KING.

*** This correspondence is now closed.—ED., *B.M.J.*

Lung Lesions in Rheumatoid Arthritis

SIR,—The problem of the systemic manifestations of the diffuse collagen diseases has engaged the attention of clinicians and pathologists for a considerable time, certainly since Finlay[1] in 1891 recognized the association between pulmonary fibrosis and generalized scleroderma. Bywaters[2] has rightly emphasized the complexity of the clinical problems arising in patients with variant patterns of the collagen diseases. In our experience "rheumatoid disease" produces such variant patterns more often than other collagen disorders solely by virtue of its higher incidence.

We cannot accept the statement made by Drs. A. Aronoff, E. G. L. Bywaters, and G. R. Fearnley (*Journal*, July 23, p. 228) that "Rheumatoid arthritis is a disease that primarily affects the joints—a local disease, affecting some joints and not others. . . ." We have, on the contrary, always regarded it as a systemic disease with local manifestations in the joints, and we speak, accordingly, of "rheumatoid disease," whose principal clinical manifestation is arthritis. We believe it is now generally established that its systemic nature may be manifested by widespread pathological changes of mesenchymal connective tissue. These occur, in some cases, in various tissues and organs, including the skin with cutaneous and subcutaneous nodules, muscles, tendons, peripheral nerves, serous structures including the synovia, pleura, and pericardium, and in some cases involving the heart, lungs, etc.

The study of the ocular effects; the refractory anaemia; the variant patterns of the disease[2 3]; the merging of rheumatoid into other systemic collagen diseases—for example, rheumatoid arthritis into polyarteritis nodosa,[4] Felty and Sjögren's syndrome,[5] rheumatoid arthritis and scleroderma[6]; the arterial pathology reported by Cruikshank,[7] and the experimental studies of Rich and Gregory[8] in respect of arterial necrosis: all such studies are calculated to broaden the approach to the rheumatic diseases and may assist towards solving the still unknown problem of aetiology. The paper of Aronoff *et al.* recognizes that there is a somewhat greater clinical and post-mortem incidence of non-specific lung lesions in a small series of patients with rheumatoid arthritis compared with a similarly small control series, but they found no evidence of examples of "rheumatoid lung syndromes" and conclude correctly that pulmonary lesions in rheumatoid arthritis must be rare. The occurrence of nodular lung and pleural lesions[9–11] is not apparently in dispute.

It is certainly also our experience that these specific lung lesions associated with sub-pleural nodules are rare, and we have been able to demonstrate them in a case[10] that came to post-mortem. We do not, however, know how commonly this occurs in life nor what would be the end effects upon the adjacent lung in patients who have experienced lung remissions from the rheumatoid process. Using routine chest *x*-rays for all patients with acute rheumatoid disease we have noted pleural effusions and peripheral lung shadows which resolve after prolonged periods and quite irrespective of treatment, and which have remained inexplicable in the face of the closest possible clinical scrutiny. Three such cases were included in our paper,[12] whose subject was pulmonary manifestations in the diffuse collagen diseases, and, moreover, the phrase "rheumatoid lung syndrome" quoted by Aronoff *et al.* was not coined by us.

Ellman and Ball,[12] recording interstitial lung changes at necropsy of two of three cases of rheumatoid arthritis, suggest that these non-specific changes may represent the end stages of the acute lung lesions which, at some stage in the patient's life, may well have been of the nodular variety.

We note that by consulting the records of necropsies conducted in their hospital on 42 cases with rheumatoid arthritis since 1936 Aronoff *et al.* found such "non-specific lesions" as bilateral adhesions in 18 cases, unilateral adhesions in 9, bronchiectasis in 5, "bronchitis" in 16. The histology of the adjacent lung in these patients is not recorded. Nor is the possible aetiology of these findings discussed, but we venture to suggest that the study of Christie[11] places pathological changes of a more specific nature in the vicinity of the abnormal structures listed by Aronoff *et al.*; and that the findings noted by these authors are precisely the type of lesion one would assume to be present in patients in whom, according to the contemporary view of the pathology of "rheumatoid disease," the nutrient arteries of the lung become irreversibly damaged.—We are, etc.,

PHILIP ELLMAN.
LEON CUDKOWICZ.

London, W.1.

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4 Ball, J., ibid., 1954, **13**, 277.
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"Over-the-Counter" Spectacles

SIR,—I was somewhat surprised to read the letter by Dr. W. S. Inman (*Journal*, July 23, p. 267). No one has ever suggested that the danger of over-the-counter spectacles is due to any injury done by their use to the eyes themselves. Many people who break their glasses on a Friday have benefited by getting a pair in this way, to cover them until they can arrange a repair or retest. No—the danger, as every ophthalmic surgeon knows, is that a patient with perhaps quite minor symptoms goes to the chain store, tests himself binocularly, gets a pair of stronger glasses which enable him to carry on for one or more years, and then, when even these prove to be insufficient, an examination by a competent person shows very advanced glaucoma in one eye and glaucoma of moderate degree in the other. That delay in diagnosis is no insignificant factor in this serious disease is emphasized by the figures shown in the Sorsby report[1] on the causes of blindness.

As it would hardly be possible to insist that no one should buy glasses over the counter who could not prove that he had had a recent examination of his eyes, and as the majority of the population cannot be expected to understand the danger as it exists, they should, in my opinion, be protected from what must appear to them as the simplest and quickest method of dealing with their reading difficulty.—I am, etc.,

O. GAYER MORGAN.

London, W.1.

REFERENCE

1 Sorsby, A., *The Causes of Blindness in England and Wales*, 1950. H.M.S.O., London.

Drowning

SIR,—In the light of Dr. K. W. Donald's fine article on drowning (*Journal*, July 16, p. 155) my own experience may be of interest. This treacherous North Cornwall coast has provided a number of casualties recently who were beyond all aid when first seen, but the cases of two patients who recovered may be worthy of record.

On September 1, 1954, a girl of 11 years was rescued from the sea. She was apparently then unconscious, and artificial respiration was carried out on the beach by another doctor (unknown). She was subsequently given oxygen and moved into bed by ambulance. Approximately one hour later she was semi-conscious, but coughing and suffering from shock. Pulse 95/min.; respiration rate 24/min.; oxygenation was good as judged clinically. The percussion note was dull at both lung bases, especially the right, and there were many medium rales at both bases, especially the right. Oxygen was discontinued and 500,000 units of crystalline penicillin given intramuscularly. Body heat was maintained with blankets but no extraneous heat source was added. During the next two hours her condition deteriorated and gave rise to acute anxiety. There was a rise of pulse and respiration rates to 148/min. and 50/min. respectively. The temperature was 99° F. (37.2° C.). Thereafter there was a dramatic improvement and she was much better the next day. Penicillin was continued, 250,000 units 6-hourly. The signs at the lung bases were demonstrable until the fourth day, when the temperature, pulse and respiration rates returned to normal. There were no sequelae.

On July 10, 1955, a male non-swimmer aged 20 was swept into deep water, where he was supported at intervals for approximately half an hour by another man who was a swimmer. On being brought to the beach he was conscious and did not require artificial respiration. He was, however, exhausted and shocked. The pulse at the wrist was impalpable, there was marked peripheral pallor and cyanosis, and there were spasms of shivering. He complained of nausea. He was kept warm and transferred to bed by ambulance. There were no abnormal chest signs. After half an hour he vomited 42 fl. oz. (1.2 l.) of watery fluid with a few food remnants. A course of prophylactic penicillin was commenced. Next day he had completely recovered.

It is considered that the first patient had inhaled a considerable amount of sea-water and later passed into so-called secondary shock. Penicillin was of great value in minimizing pulmonary complications. The second patient demonstrated the protection of the lungs by the swallowing of sea water in a non-swimmer during periods of submersion.—I am, etc.,

D. W. BALDWIN.

St. Merryn, Cornwall.

Chronic Rectal Bleeding Due to Milk

SIR,—The case history presented under this heading by Drs. F. P. Antia and S. H. Cooper (*Journal*, June 11, p. 1416) strongly suggests a condition of chronic ulcerative colitis. (Seven years previously the patient had had a disease episode with semi-solid stools containing mucus and frank blood not too well mixed.) Although the allergic features in this case cannot be denied as aetiological factors, it is necessary to consider the patient's personality as a whole and to stress the psychological viewpoint. The history of this case shows an unhappy marriage with a short-tempered, apparently domineering husband using physical violence at times.

Several papers dealing with the psychosomatic aspects of the condition describe patients as being involved in situations to which it was difficult or impossible to adjust. Conflicts centring around marital relationships have been especially stressed as precipitating factors. As to the physiological aspects of the disease, the initial localization of the ulceration is always in that part of the large bowel supplied by the sacro-pelvic portion of the parasympathetic. It is believed, though not proved, that lysozyme, a mucolytic enzyme, increases through parasympathetic stimulation due to emotional stress and deprives the mucosa of its protective mucin, so that it becomes vulnerable to the tryptic enzyme present in the intestinal tract. As to the episode seven years ago mentioned in the case history, when "malingering was suspected because her husband was not treating her well at home, and traumatic bleeding from the rectum was supposed to be her device to stay in hospital," I would not assume malingering, but I would not rule out digital manipulation of the rectum as an expression of anal regression. A case with similar features, though on a psychotic level, will be reported by the writer, Forster, and Schlichther in the *Canadian Medical Association Journal*.—I am, etc.,

MILO TYNDEL.

Brandon, Manitoba, Canada.

Obituary

J. B. CHRISTOPHERSON, C.B.E., M.D. F.R.C.P., F.R.C.S.

Dr. J. B. Christopherson, who died at his home at Lydney-on-Severn on July 21, made some important contributions to the knowledge of tropical diseases. He was 87 years of age.

John Brian Christopherson was born at Batley, Yorkshire, the son of Canon Brian Christopherson, rector of Falmouth. From Clifton College he went on to Caius College, Cambridge, and continued his medical training at St. Bartholomew's Hospital. After graduating M.B., Ch.B. in 1893 he held the posts of house-surgeon, house-physician, and demonstrator of anatomy at St. Bartholomew's Hospital. In 1897 he took the F.R.C.S. and in the following year proceeded to the M.D. of Cambridge. For six years, from 1896 to 1902, he was on the surgical staff of the Albert Dock Hospital, but he went out as a surgeon to the Imperial Yeomanry Hospital, Deelfontein, during the South African War, and it was many years before he returned to work in England. In 1902 he was appointed physician to the Governor-General of the Sudan, and two years later became Director of Medical Services to the Sudan Government. He resigned these appointments in 1909 to become Director of Civil Hospitals at Khartoum and Omdurman. By this time he had transferred his main clinical interest from surgery to medicine, and he took the M.R.C.P. in 1905, being elected F.R.C.P. in 1913. During the years before the first world war Christopherson investigated many of the tropical diseases common in the Sudan, describing his findings in several papers he wrote at this time. It was in 1918 that he first reported in this and other journals the use of intravenous injections of antimony tartrate as an effective treatment for bilharziasis. During the first world war Christopherson went with a Red Cross unit to Serbia, where he was taken prisoner of war by the Austrians. On his release he went to France, serving as secretary to the War Office Commission on Medical Establishments in the British Expeditionary Force. He was appointed C.B.E. in 1919 and he was also the holder of the Order of the Nile (third class) and the Order of St. Sava. After the war he settled in London and was for a time in charge of the special bilharzia clinic of the Ministry of Pensions. He was an examiner in tropical diseases to the Royal College of Physicians and to the University of London, and was medical adviser to the Universities' Mission to Central Africa. Though Christopherson did not lose his interest in tropical medicine—he was physician for tropical diseases to the Royal Masonic Hospital and in 1929 was elected president of the Tropical Diseases Section of the Royal Society of Medicine—nevertheless as the years went by he turned his attention more and more to diseases of the lungs, and he became a member of the staff of the London Chest Hospital, Victoria Park. In particular he wrote several papers on the subject of asthma and chronic bronchitis which were published in this *Journal*. He retired from active practice some years before the second world war and went to live in Gloucestershire.

Dr. Christopherson married in 1912 Joyce Eleanor, daughter of the late Dr. J. A. Ormerod, physician to St. Bartholomew's Hospital.

We are indebted to Sir PHILIP MANSON-BAHR for the following appreciation. J. B. Christopherson—"Christo" to his friends—has passed on at the advanced age of 87. His name is but a memory to the present generation, for he had been living in retirement in his country home, appropriately named "Heaven's Gate," for nearly twenty years, yet his fame is known to all students of tropical medicine. To Christopherson is undoubtedly due the modern treatment of schistosomiasis with antimony: he was the first to put this method on a proper basis. It is only fair to him that the facts should now be set forth, as they are apt to be forgotten. The revival of antimony as a medicinal drug was due to Sir Leonard Rogers, who gave intravenous injections of sodium antimony tartrate (tartar emetic) to patients suffering from kala-azar in Calcutta in 1912 and was able to prove that this disease, hitherto regarded as incurable, could be cured. In 1917 Christopherson, who was then in Khartoum in charge of the Civil Hospital, had several cases of kala-azar under his care which were also infected with schistosomiasis (*Schistosoma haematobium*). He observed with astonishment that not only did the former disease respond to the antimony injections but that also the schistosome eggs disappeared gradually from the urine. At the same time he observed structural changes in the ova themselves: they became dark and opaque and no longer "hatched" when placed in warm water, as normal eggs are prone to do. He found that the contained miracidia were in fact dead, and suggested that the antimony had a direct action upon the female schistosomes themselves, a hypothesis which has since been proved to be correct. This discovery was at that time received with astonishment because it was generally held that schistosomiasis (bilharziasis) was incurable on account of the structure and location of the adult parasites.

I was fortunate to be able to visit him in April, 1919, in Khartoum, where he most convincingly demonstrated his technique of injection and the results he had obtained. Up to this time I had nursed considerable apprehension in giving intravenous injections of antimony to anybody on account of the violent reactions which I had seen during the treatment of trypanosomiasis in the period before the outbreak of the first world war. It should be stated that this work of Christopherson's was quite original, and it was only when the results had been published that he became aware that J. E. R. McDonagh had claimed to have cured two cases of urinary schistosomiasis by antimony three years previously.

From this time onwards I was to see a great deal of Christo. He was a kind, considerate soul, with a keen, inquisitive look and an inquiring mind. When circumstances warranted it he could be surprisingly stubborn and tough. There were occasions when he was criticized for his work on spirochaetosis of man and fowls in Khartoum by those in authority in the Sudan, but he stuck to his point and won.

He played a great part in the medical history of the Sudan. He was a friend, medical attendant, and confidant of Slatin Pasha, Inspector-General of the Sudan. This connexion stood him in good stead, because when Christopherson was a prisoner of war in Austria in 1916, Slatin (who was an Austrian and had retired to his country on the outbreak of war) came to his rescue and secured his release. He was also a friend of Sir Reginald Wingate, who succeeded Lord Kitchener as Sirdar in 1899.

At the end of the first world war Christopherson returned to London and worked as a consultant. He was given charge of the bilharzia clinic of the Ministry of Pensions and was responsible for the treatment of the large number of ex-Service men who had contracted this infection during the war. To the surprise of all his friends he took up the specialty of pulmonary diseases and became consultant to the London Chest Hospital, Victoria Park. On many occasions it fell to my lot to act as co-examiner with him in the Diploma of Tropical Medicine, and was able to realize his wide range of knowledge, not only of tropical diseases but of medicine in general. One had always to

bear in mind that he was highly qualified, being a Fellow of both Colleges, and that it was only by an accident that he was not on the teaching staff of the London School of Tropical Medicine, since he was one of the originals of that institution, having been surgeon to the Albert Dock Hospital for six years from 1896 to 1902. We shall all mourn the passing of Christo for a man of great worth and great attainments, who became a guide, philosopher, and friend to all who came into contact with him.

H. J. McCURRICH, M.S., F.R.C.S., M.R.C.O.G.

Mr. H. J. McCurrich, senior consultant surgeon at the Royal Sussex County Hospital, died at his home at Hove on July 16 after a long illness borne with great fortitude. He was 64 years of age.

One of four children of the late John Martin McCurrich, chief engineer of the Bristol and Avonmouth docks, Hugh James McCurrich was born on August 3, 1890, and was educated at Clifton College, Bristol University (for which he played Rugby football), and at St. Bartholomew's Hospital. He qualified M.R.C.S., L.R.C.P. in 1915 and then joined the Army as a combatant officer in the Middlesex Regiment, later serving as a captain in the R.A.M.C. until he was invalided out after an attack of trench feet. He resumed his civilian medical career at St. Bartholomew's first as house-surgeon to the late Sir D'Arcy Power, and later as resident midwifery assistant and demonstrator of obstetrics. He took the London degrees of M.B., B.S. in 1922, and in the following year proceeded to the M.S. and became a Fellow of the Royal College of Surgeons of England. After further resident appointments at the West London, Putney General, and Royal Masonic Hospitals, he was appointed resident surgical officer at Sheffield Royal Hospital. From Sheffield he went to Brighton in 1925 as medical superintendent of the Brighton Municipal Hospital, later known as the Brighton General Hospital. This was an admirable appointment, for it gave scope to McCurrich's considerable clinical and administrative abilities and to him was mainly due the complete transformation which took place in the institution during his term of office. A generous tribute to his services in this connexion was paid by the Brighton public assistance committee when he relinquished the post in 1931. He was awarded the Rogers prize by the University of London in 1926 for his essay on the treatment of the sick poor in this country; in this he sketched the development of hospital and public medical service from Saxon days to contemporary times. He foresaw much of the pattern of development of the hospital service which became an accomplished fact twenty years later. After serving two years as surgeon to the Hove General Hospital he was appointed assistant surgeon to the Royal Sussex County Hospital in 1931, becoming gynaecologist also in 1939 and full surgeon in 1946. He was also consultant surgeon to the Victoria Hospital, Lewes, and he continued to serve for some time as consultant surgeon to the Brighton General Hospital. He was elected M.R.C.O.G. in 1935.

McCurrich was chairman of the Brighton Division of the British Medical Association from 1938 to 1941; he also served on the Council at Headquarters for one session (1943–4) and on a number of committees of the Association, including the Central Consultants and Specialists Committee from 1943 to 1947 and again from 1952 up to the time of his death; and he represented his constituency in the Annual Representative Meeting several times between 1938 and 1943. He was president of the Brighton and Sussex Medico-Chirurgical Society in 1946–7, the centenary session of the society, taking for the title of his presidential address "The First Hundred Years." This was a most valuable and interesting account of political and social conditions at the time the society was founded in 1847, of the outstanding medical achievements during the century which followed, and of the society's reaction to the discoveries of this epoch. By a happy thought and through the courtesy of the borough authorities the meeting was held in the council chamber of the town hall, the building in which the first meeting of the society took place in 1847. The subsequent dinner of the society was honoured by the presence of the Presidents of the three Royal Colleges.

In 1944 McCurrich founded the Association of the Honorary Staffs of the Major Non-teaching Hospitals of England and Wales, being impressed by the need for an association to represent these staffs during the discussions then taking place before the passing of the National Health Service Act of 1946. Never a man to be deflected from any task to which he put his hand, he succeeded in establishing this association on a sound basis, and he was its first president from 1944 to 1947 and again when the association took its present title of the Regional Consultants and Specialists Association during 1949–50. Few men could have achieved such a success in the midst of a busy professional life. He was a member of the Brighton and Lewes hospital management committee from its formation in 1948 until his death and chairman of the group medical committee from 1948 until March this year.

Though so actively engaged in medico-political affairs, McCurrich never allowed his professional work to suffer, and he won the respect and affection of a very wide circle in his profession. Both the Royal Sussex County and the Brighton General Hospitals owe much to his energy and devotion. He made many contributions to medical literature, always interesting and often original and with a happy gift of humour. His chapter on gynaecological procedures in Pye's *Surgical Handicraft* and an article in the *Journal of the International College of Surgeons* of September, 1954, on "A method of restoration of the bile flow after damage to the common bile duct" may be mentioned as among the more important. Always outspoken and fearless and somewhat impulsive in nature, his life was a hard one, for the burden of work which he undertook was enormous, and he suffered many discouragements without flinching. Few men could have carried this load with such apparent ease. Though stricken with a mortal disease, he carried on to the end, to the amazement and admiration of his many friends. He had many interests outside his profession, in particular sailing, and he found time for social work at the Brighton Boys' Club, of which he was vice-president. His first wife, formerly Dorothy Bettine Ellis, died in 1951, and he is survived by his second wife, formerly Norah Shaw, and by the two sons and a daughter of his first marriage.—J. R. H. T.

C. E. D. writes: Hugh McCurrich will always be remembered as a staunch and steadfast friend. In all relations with his patients he was invariably a conscientious doctor and a skilful surgeon. He was sure of his experience, yet always keeping an open mind for new ideas from whatever quarter they might come. He never made any claims to literary talent, yet wrote clearly and forcibly and always to

the point. When speaking in public he was forthright yet restrained, capable of expressing the common-sense point of view most effectively.

He appeared always to be complete master of himself and all his affairs. It would seem unthinkable that he should even ask for any concession, advantage, or privilege for himself. While strict towards himself, he was always charitable to others. Though fully aware of human proneness to error, he was always willing to look beyond this to the solid and good in other people, however deeply it might appear to be buried.

In his last illness he showed an unforgettable example of manly courage, continuing quietly at work, seeking to restore to others the good health which he well knew was now denied to him. He never complained, and tried hard to smile even when in pain. When his name is mentioned his friends will always recall his upright carriage, his cheerful expression, his strong, confident voice, his genial good humour, his sound common sense, yet rare and delicate gentleness.

Dr. ERIK WALLER, who died on January 28, aged 79, was a surgeon in charge of a provincial hospital in Sweden. His career as a surgeon was not particularly distinguished, and he published only one minor work on surgery. But as a student of the history of medicine, with a genius for collecting works on this subject, he towered over his compatriots and came to enjoy a well-earned international reputation as the creator of one of the finest collection of old medical works in the world. Between 1910 and 1950 he amassed a library of more than 20,000 volumes, many of them unique and of priceless value. Among his many friends and competitors for rare books on the Continent and the U.S.A. was Cushing, with whom he often ran a neck-and-neck race for bibliophilic prizes. On one occasion Waller received from the U.S.A. a catalogue of books for sale. One of them was a copy of the first edition of Harvey's *De Motu Cordis* (1628, Frankfurt). Waller knew very well where each of the few numbers of this edition was to be found, but he could not place this particular copy. With vague forebodings he went to the bookshelf in which he knew his own copy had been placed. Its place was empty. Fortunately he knew his own copy in and out, and could refer to markings on it page by page. Cushing's aid was now invoked, and pressure was exerted on the latest possessor of the book to disgorge his prey. The original culprit proved to be a compatriot and colleague, now dead, of Waller, whose hospitality had been abused by a guest so appreciative of the value of this specimen that he pocketed it surreptitiously and later on sold it in England. When Waller resigned his appointment as surgeon in Lidköping in 1940 he retired to Stockholm and was elected librarian to the Swedish Medical Society. Here he delighted in demonstrating rare works to colleagues interested in the history of medicine. He continued all the time to add to his own library, but, as he often remarked, times had changed. Early in his career valuable works on the history of medicine were numerous, prices were modest, and the field of competitors was small. Now such works have become relatively scarce, prices have soared, and the number of competitors is legion. Many years ago Waller had pined for a copy of the first edition of Linnaeus's *Systema Naturae*. It was Cushing who forestalled him. Quite recently another copy came on the market at Sotheby's in London, but now the price was prohibitive. With Cushing's library bequeathed to Yale, it was fitting that Waller's library should be enjoyed by his compatriots, and it has now become the property of Upsala University. A complete two-volume catalogue of his library is shortly to be published (see *B.M.J.*, 1954, **2**, 1018). Waller was the recipient of many honours at home and abroad, from countries including Italy, Germany, England, France, and the U.S.A. His latter years were clouded by progressive heart disease, and of late he had been confined to bed suffering from lassitude and general malaise.

Medical Notes in Parliament

Scottish Health

Aspects of health in Scotland ranging from the care of aged people to the new hospital building programme were discussed in the House of Commons on July 19.

Miss MARGARET HERBISON (Lanarkshire, North, Lab.) set out the things that should be done for old people as adequate money to enable them to live in their own homes, provision of houses suited to their needs in every local authority scheme, extension of the home help service (particularly at night), a better provision of meals to old people in their own homes, and the availability of a chiropody service. For those for whom residential homes must be made there had been a great improvement since 1948, but it was far from adequate. Mrs. JEAN MANN (Coatbridge and Airdrie, Lab.) said that in 1953 there were in Scotland 1,134 deaths from accidents in the home and 600 from road accidents; in 1954 the figures were 1,106 and 561. Scotland suffered more than other parts of the British Isles from overcrowding, and it was largely from that that accidents in the home arose. A surgeon with whom she was intimately acquainted, and who worked in the Royal Hospital for Sick Children, Glasgow, constantly told her to let mothers know that they ought to put girls in pyjamas; 38% of deaths from burning were due to the wearing of nightdresses. Mirrors ought not to be put above fireplaces. Home accidents occurred mainly to children under 5 and old people over 65—and among the old people the accidents were usually from falls rather than burns. Mr. THOMAS HUBBARD (Kirkcaldy Burghs, Lab.), speaking on the need for greater research into the causes and treatment of coronary thrombosis, commended the introduction in Fife and Kilmarnock of a voluntary scheme of making the disease notifiable, but urged that it should be extended to include the large burghs of Kirkcaldy and Dunfermline. Mr. THOMAS OSWALD (Edinburgh, Central, Lab.) gave an account of a recent survey of elderly persons in Edinburgh, in which 159 doctors took part and 5,086 persons were included. Records kept over a month showed that 40% of the old people had some kind of need. 1,270 required medical attention; 1,274 required home or domestic assistance. Of the first group, 301 were living alone, 17 were bedridden and 72 restricted; 320 lived with the spouse only, and of these 44 were bedridden and 112 restricted. The survey disclosed that there were 658 cases needing institutional care, 217 of them living alone. When that was considered as only a partial survey in Edinburgh, it was alarming to think of the numbers that must be similarly placed in Glasgow, Dundee, Aberdeen, Kirkcaldy, and other towns.

Hospital Building Programme

Mr. NIXON BROWNE, Under Secretary, Scottish Office, in his reply to the debate, gave up-to-date details of the new hospital building programme announced last February, about which there had since been consultations with the regional hospital boards. At the Western General Hospital, Edinburgh, the main part of the radiotherapy institute of 100 beds for malignant diseases was practically complete, and work was proceeding on a new unit of 60 beds for neurosurgery. The two schemes together involved £640,000. In the 1955–6 programme three major projects were to be started—reconstruction of Westgreen Mental Hospital, Dundee (cost £250,000); a surgical unit of 120 beds at the Victoria Hospital, Kirkcaldy (£450,000); and a new hospital at Bellshill, Lanarkshire (£500,000). For mental deficiency work three major development schemes, providing about 850 additional beds, were to start next year—at Ladysbridge, near Banff; Baldowan Institution, near Dundee; and the Royal Scottish National Institution at Lambert. Together they would cost about £1,200,000, and take four or five years to complete. For the third year, 1957–8, planning

was already in hand on three major schemes due to start then—a radiotherapy and research unit at Glasgow Western Infirmary, a large-scale reconstruction of the Royal Mental Hospital, Edinburgh, and a replacement of the Gilbert Bain Hospital, Lerwick. These schemes involved a capital expenditure of about £4m. In addition, the regional hospital boards would be carrying out their own projects at a rate involving expenditure of about £1,300,000 a year.

He agreed it must be recognized that these were deficiencies to be made good in the services provided for old people, and referred to the report of the Department of Health for 1954 for indications of recent progress in providing hospital accommodation. The department was anxious that the local authority services which could help the old people to live at home should continue to develop.

Mental Defectives

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on July 18 if he would state the number of persons in England and Wales who, during 1952 and 1953, were certified as of unsound mind and admitted to involuntary detention in mental hospitals on Summary Reception Orders made under Sections 14 and 16 of the Lunacy Act, 1890, as amended by the National Health Service Act, 1946; and what proportion of these were admitted directly into mental hospitals, and what proportion after an intermediary period in the mental observation ward of a general hospital. Mr. IAIN MACLEOD stated that certified patients admitted to mental hospitals during 1952 and 1953 totalled 20,297 and 20,579 respectively. Of these totals the proportions admitted after a period of observation in a general hospital were respectively 16.92 and 15.69%. Dr. JOHNSON said that most of the admissions under these sections were direct into mental hospitals. It had been stated by a number of prominent medical psychiatrists that in spite of the warnings of the last Royal Commission certification of people suffering from temporary delirium, and their consequent detention in mental hospitals, was still taking place. Mr. MACLEOD said the original question had asked for those who spent an intermediate period in the mental observation wards of a general hospital. There were in addition a great number of patients who spent a period in the observation wards of mental hospitals, which would put rather a different complexion on the figures. That was a proportion he would like to see increased. Mr. KENNETH ROBINSON (St. Pancras North, Lab.) said there was a considerable difference of professional opinion about the whole desirability of observation wards. Would the Minister consider a departmental committee of inquiry? Mr. MACLEOD replied that there was a difference of opinion about almost everything in the Health Service.

The MINISTER OF HEALTH gave Mr. J. BARTER (Ealing, North, Con.) figures (divided by regions) showing that at the end of 1954 the numbers of defectives notified as being in need of hospital care and still awaiting admission were: low grades: urgent, 2,137, non-urgent, 1,449; others: urgent, 1,863, non-urgent, 2,284.

The regional figures were:

Mental Defectives in Need of Hospital Care and Still Awaiting Admission on December 31, 1954

Region	Low Grades		Others	
	Urgent	Non-urgent	Urgent	Non-urgent
Newcastle	203	211	142	357
Leeds	111	60	167	128
Sheffield	328	250	189	265
East Anglia	164	12	91	53
North-west Metropolitan ..	76	32	146	128
North-east ,, ..	105	88	133	241
South-east ,, ..	177	242	34	48
South-west ,, ..	187	141	97	184
Oxford	86	53	76	90
Bristol	35	31	23	42
Wales	107	136	271	493
Birmingham	270	105	113	120
Manchester	187	57	250	94
Liverpool	101	31	131	41
Total ..	2,137	1,449	1,863	2,284

Short-term Care

Mr. BARTER asked if the Minister was satisfied that accommodation available for short-term care of mental defectives was fully utilized by local authorities. Miss HORNSBY-SMITH, Parliamentary Secretary, informed him that, during 1954, 1,700 mental defectives were received for short-term care in hospitals and 461 elsewhere. Ninety local health authorities in England and Wales had power in schemes approved under s. 28 of the National Health Service Act to maintain defectives in these circumstances. No specific amendment of schemes was needed to enable them to secure removal to a hospital. She did not think another circular was called for. Each year there had been an increase in the number of patients for whom these facilities were arranged.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked why no annual report was made of these statistics. Miss HORNSBY-SMITH explained that sometimes when permanent patients were allowed out on holiday the bed was made available for a patient staying for a short period. There were no permanent statistics of the availability of beds on that basis, but there was a record of the number of people able to make use of such facilities.

Poliomyelitis Vaccine

In a reply to Mr. JOHN RANKIN (Glasgow, Govan, Lab.) Mr. J. R. BEVINS stated on July 25 that it was proposed to send an investigator to the Gambia to study the possibility of finding strains of virus occurring naturally among the relatively immune local population which might be suitable for inclusion in an improved form of the Salk vaccine. He also stated in a reply to Mr. C. R. HOBSON (Keighley, Lab.) that the Medical Research Council was at present studying the feasibility of transporting monkey kidney tissue to this country for use as a culture medium for growing poliomyelitis virus. No arrangements had yet been made for importing live monkeys from areas outside India, but the possibilities were being investigated.

Experiments in Hospital

Mr. S. SWINGLER (Newcastle-under-Lyme, Lab.) asked the Minister of Health on July 25 what was being done by his department to prevent the conduct of medical experiments with harmful effects on the patients concerned. Mr. IAIN MACLEOD said that he had nothing to add to the answer given on February 14 (*Journal*, February 26, p. 546), which had been brought to the notice of the responsible officers of hospital boards.

Mr. SWINGLER said there were still on occasion reports in the medical press of experiments with new drugs with known harmful effects. Would the Minister ask those responsible for research to put a check on those who perhaps were going a little too far? Mr. MACLEOD said that he did arrange for the matter to be brought to the notice of senior medical officers of regional boards and secretaries of boards of governors. They were given copies of a confidential memorandum issued by the Medical Research Council to the staff engaged on this research. If that needed following up he would see that it was done.

Insurance Policy Certificates

Mr. J. A. SPARKS (Acton, Lab.) asked if the Minister of Health was aware of the growing practice of some insurance companies who, without requiring medical evidence, insured the lives of old-age pensioners who at the time were suffering from diseases which invalidated the claim; and if in these circumstances he would relieve medical practitioners from the duty of supplying insurance companies with certificates of the cause of death. Miss PAT HORNSBY-SMITH, Parliamentary Secretary, replied "No." The Minister was not aware of any statutory obligation on medical practitioners to supply insurance companies with certificates of the cause

of death. Any obligation on a doctor to supply a certificate to an insurance company was a matter of arrangement between the doctor and the company, and was not a statutory obligation.

Hearing-aid for Children.—If the report on the trials of the new model hearing-aid for children (Monopak OL44X) is favourable, distribution should start next summer..

Surgical Boots.—During 1954 there were 49,689 pairs of surgical footwear supplied in England and Wales. The average time for delivery is two and a half months from first measurement to final fitting.

Invalid Motor-cars.—The estimated additional capital cost of an invalid motor built to carry two people instead of one is £75, and the additional maintenance charge £40.

Radioactivity Protection.—The radioactive substances advisory committee has submitted to the Minister of Health a code of practice for the protection of persons working with ionizing radiations in hospitals. He is considering it, and hopes to be able to publish it soon.

Returned Empties.—Chemists are remunerated for all containers (including medicine bottles) by a flat-rate payment for each prescription dispensed. The approximate cost in England and Wales during 1954 was £1,138,000. A system of returnable deposits has often been considered, but not thought practicable.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on June 11 the following degrees were conferred:

M.D.—F. R. R. Martin, H. P. Lambert, C. B. McKerrow, D. Bulmer, L. Haas, R. A. Struthers.

M.CHIR.—J. O. Robinson.

M.B.—A. Pollard, D. C. L'E. Burges, J. O. Robinson, R. J. Haythornthwaite, June P. Brady.

UNIVERSITY OF MANCHESTER

The following candidates have been approved at the examinations indicated:

CH.M.—R. T. Grime.

FINAL M.B., CH.B.—H. Fox (with honours and distinction in medicine), I. B. Houston (with honours), D. Mayor (with honours and distinction in surgery), H. Allison, J. C. Bell, Wendy Bellhouse, A. J. Benson, M. Bourke, R. M. Briggs, D. H. Bunting, A. D. Calderbank, G. Caplan, L. M. Carter, M. A. Casson, C. B. Cohen, E. P. Copp, G. A. Davenport, B. B. Done, Mrs. Jean Dubberley, P. Dutton, P. J. Ellis, F. Fletcher, Beryl M. Foley, P. Garner, A. O. Griffiths, A. Hargreaves, G. Hartley, G. M. Hunter, J. P. Lawson, S. G. Leech, J. S. McGrail, N. D. Royle, A. Rushton, P. F. Schofield, J. Southern, T. W. Stewart, T. B. Stretton, Teresa M. Swift, M. R. Thompson, F. J. Unsworth, E. Unwin, M. J. Viney, Mary R. Walker, Mrs. Kathleen Whale, Lois R. Whyatt, Freda Young.

UNIVERSITY OF BIRMINGHAM

The title of University Research Fellow has been given to the following during the tenure of their present posts in the Department of Medicine: Dr. S. H. Taylor, Medical Research Council Fellow in Clinical Research; Dr. J. M. French, Mackenzie Mackinnon Research Fellow.

Dr. M. Sim and Dr. R. W. Tibbetts, Clinical Lecturers in Psychiatry, have been appointed part-time Lecturers in Psychological Medicine, and Dr. R. F. Crampton Lecturer in Physiology, all from October 1, 1955.

In Congregation on July 2 the following degrees were conferred:

M.D.—W. T. Cooke (with honours), B. MacMahon (with honours), H. G. H. Richards.

PH.D.—F. A. Smith, M.B., Ch.B., A. G. W. Whitfield, M.D., F.R.C.P.

M.B., CH.B.—[1] [2]Molly Hill (with second-class honours), Jean E. M. Baron, Brenda L. Bodenham, F. S. Boi-Doku, [2]Ann D. Braham, Jeanne L. Brough, G. T. Brown, K. G. Buckler, P. J. Chaudoir, J.-G. Chitnis, A. E. Cutler, T. S. Dogra, J. L. Dyke, Elizabeth A. Fisher, Christine M. Fitzgerald, C. B. Franklin, [1]Elizabeth George, [2]J. D. Goode, C. M. Green, P. Hall, Sheila P. Hancock, B. Hansell, A. J. Harbott, [4]M. A. Harper, Pamela A. Harris, B. G. Harevin, J. Haslam, C. N. Haynes, [2]R. W. Heslop, Margaret W. Hill-Owens, J. R. Holliday, [4]G. Horn, Julia C. Hurford, G. T. Kelley, J. N. Kille, D. G. Larard, J. D. Leng, [4]L. Lewis, H. McD. Liegeois, M. B. Love, Mary L. Mackay, R. B. Miller, Valerie E. Millward, Mary G. M. Moss, P. M. Moss, S. H. Nicolaides, [1]G. D. Officer, A. L. Parker, A. W. Parkes, J. L. Pearce, [3]D. C. Pearson, E. Peters, D. M. Price, [1]B. B. Reid, R. F. Reynolds, M. T. Rigby, R. O. Rimmer, [3]M. Li. Rutter, F. Sayer, Betty V. Scott, R. C. Shapiera, Helen R. Sharples, R. Summerly, R. Tinkler, J. A. Tooth, G. J. Varley, [3]D. M. Ward, M. S. Warwick, J. L. Webster, Myrtle E. White, B. N. Williams, M. A. Woodhouse, and, *in absentia*, Denise J. Duchesne.

The following scholarships, etc., were awarded in the Faculty of Medicine:

Queen's Scholarships.—Final year, Molly Hill; Fifth year, W. A. Lishman. *Ingleby Scholarships*, Elizabeth George (obstetrics and gynaecology), R. W. Heslop (paediatrics and child health). *Special Undergraduate Scholarships*, M. F. Grayson, A. Rhodes, P. M. Worrall. *Arthur Foxwell Memorial Prize in Clinical Medicine*, M. A. Harper. *Sampson Gamgee Memorial Prize in Surgery*, Elizabeth George. *Joseph Sankey Prize in Clinical Surgery*, G. T. Brown. *Beckwith Whitehouse Prize in Obstetrics and Gynaecology*, B. B. Reid. *Cyril Raison Prize in Surgical Diseases in Children*, R. W. Heslop. *Russell Memorial Prize in Nervous Diseases*, Ann D. Braham and Molly Hill. *Priestley Smith Prize in Ophthalmology*, J. L. Pearce. *Douglas Marsh Ear, Nose and Throat Prize*, Molly Hill. *Leith-Newman Prize in Pathology (Medicine)*, C. T. Dollery and W. A. Lishman. *Bostock Hill Memorial Prize in Social Medicine*, H. G. Schroeder. *Bertram Windle Prize in Anatomy*, A. D. Barnes and R. St. J. Glydon. *Peter Thompson Prize in Anatomy*, J. Herbert.

[1]Distinction in obstetrics and gynaecology. [2]Distinction in paediatrics and child health. [3]Distinction in pharmacology and therapeutics. [4]Distinction in forensic medicine and toxicology. [5]Distinction in medicine.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

M.D.—E. T. Downham, C. H. Jones, R. B. McConnell, R. H. Martlew, J. Parkhouse, Patricia M. Russell.

M.B., Ch.B.—Gwendoline M. Clayton (with first-class honours and distinction in surgery and in obstetrics and gynaecology), Norma S. Strelitz (with second-class honours and distinction in surgery), Sheila I. Angles, Edna W. Anthony, J. E. Barclay, A. V. Basil, R. E. Blair, B. K. Brooker, J. B. Cardwell, W. J. Carter, W. H. Cookson, J. L. Crane, R. B. Crosbie (with distinction in obstetrics and gynaecology), J. A. Culshaw, E. E. Cureton, Pamela A. Deane, A. G. Edwards, O. Edwards, G. P. Evans, G. H. Evans, Mary D. Evans, Wendy A. B. Fairhurst, P. W. Ferguson, A. Fowden, Elizabeth A. Gillberry, Patricia M. Hastie, J. P. Hawe, E. Hershon, Audrey M. Hillary, A. L. Hodgson, J. D. Jones, M. V. Jones, R. Kellner, Emily M. Kerr, Barbara J. Legsom, Nancy G. Lord, Margaret H. Macaulay, D. H. Macleod, Sheila G. Maddock, Yvonne G. R. Malmbir, M. D. Manson, Sheelagh P. Marsh, C. Maxwell, J. Meecham, Alicon V. Milles, J. G. Morris, Patricia A. Morris, Shirley P. K. Morris, D. S. Orr, J. P. O'Shea, T. Owen, I. F. Quayle, D. R. Raw, Pamela A. Roberton, D. V. Roberts, J. T. Roberts, N. O. Roberts, Muriel G. Robinson, Mary M. Scott, G. M. Simpson, D. J. Smyth, B. E. Stober, Margaret M. Summers, Josephine E. M. Topping, G. H. Ungar, P. D. B. Wallice, P. Watson, R. E. Wild, C. W. L. Williams, K. Wilson, Elizabeth A. Witham, Mary C. Wood.

DIPLOMA IN PUBLIC HEALTH.—Jessie I. Anderson, S. M. Bieber, Sheila C. Blackburn, Barbara Briggs, R. D. Choudhury, Diana Daniel, Phyllis J. Disley, O. L. Evans, R. G. Hendry, Irene Lynch, C. A. McKeagney, R. S. Male, T. O'Shea, F. Seymour, J. M. Sword, J. C. Taylor, A. H. Wilde.

DIPLOMA IN RADIOLOGY.—*Radiodiagnosis*: A. Bhattacharyya, Constance M. Davis, H. E. Jones, J. P. Murray, I. P. Smyth. *Radiotherapy*: B. B. Roy.

UNIVERSITY OF LEEDS

The following degrees were awarded in the Faculty of Medicine in June:

M.D.—A. S. Woodcock (with distinction).

M.B., CH.B.—Margaret Gatecliff.

UNIVERSITY OF SHEFFIELD

The following full-time appointments are announced: Dr. P. Anderson and Dr. N. E. Shaw, Demonstrators in Anatomy; Dr. K. D. Neame and Dr. F. A. Jenner, Assistant Lecturers in Physiology; Dr. W. D. Smith, Research Assistant in Medicine.

Dr. D. A. J. Tyrrell has been appointed part-time Honorary Lecturer in Medicine; and Dr. J. D. S. Hammond part-time Tutor in Medicine for Dental Students.

Dr. J. B. Coakley has been appointed part-time Honorary Demonstrator in Anatomy.

UNIVERSITY OF BRISTOL

Dr. J. F. Lyons has resigned his appointment as Clinical Teacher in Psychiatry.

The following candidates have been approved at the examinations indicated:

M.D.—M. E. M. Herford, H. Schnieden.

CH.M.—P. R. Slade.

M.B., CH.B.—[1] [2]Elizabeth Burge, [1] [3]Joyce E. Moore, [1] [3]Mavis M. Polkinghorne, G. K. Allwood, Dorothy F. Bate, Jean M. Bebell, Prudence M. Beckingham, H. F. Bolton, M. T. Charleston, Margaret E. Chesterfield, J. P. J. Clarke, Shirley A. Craven, Edith Palerman, F. G. Farrelly, D. J. Foley, J. K. Hartwell, A. J. S. James, Mary T. C. A. Jorro, P. M. Lambert, Pamela M. Laurence, Penelope A. Leighton, [2]Nancy Mercer, R. E. Midwinter, G. A. Naylor, [2]J. B. Neilson, H. J. L. Nicholls, P. J. Roylance, [4]D. W. Simpson, E. M. Smith, Anne L. Stewart, E. Wallace. *In Group I completing the examination*: Janet H. Keevil, R. G. McCormick. *In Group I only*: I. M. Joiner, J. H. Williams.

D.P.H.—*Part II*: Margaret M. J. O'Dea, Elizabeth M. Sefton, P. J. Speller, M. D. M. Reilly.

[1]With second-class honours. [2]With distinction in public health. [3]With distinction in medicine. [4]With distinction in obstetrics and gynaecology.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the Faculty held on July 4, with Professor Stanley Alstead, Visitor, in the chair, T. Gibson and H. E. Hutchison were admitted Fellows of Faculty.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College held on June 3, with the President, Dr. Edward T. Freeman, in the chair, the following Members were admitted to the Fellowship of the College:

P. B. B. Gatenby, S. D. McGrath, M. A. Majekodunmi, M. G. Nelson, H. O'Flanagan, P. P. O'Malley.

The following were admitted to the Membership:

P. A. Farrelly, E. W. Knox, J. Lowry, D. H. Merrin, Eleanor T. Rolston.

SOCIETY OF APOTHECARIES OF LONDON

The Master, Sir Cecil Wakeley, who presided at a meeting of the Court of Assistants of the Society on June 21, was re-elected as the Society's representative on the British Postgraduate Medical Federation, and Dr. Roche Lynch on the committee of management of the Chelsea Physic Garden.

It was reported that the late Mr. Philip Turner, Liveryman, had bequeathed £100 to the Society.

The Lord Mayor and the Sheriffs were present at the dinner which followed the Court.

The following candidates, having completed the final examination, have been granted the diploma of L.M.S.S.A.:

D. P. Addy, G. M. Fraser, K. A. Huang, F. John, E. de M. Taunton, J. M. Forster, V. J. Jobson.

The following candidates were awarded the diploma of Master of Midwifery:

D. B. Brown, F. J. Cockersole, S. A. Smith.

Vital Statistics

Glandular Fever at Royal Free

By Tuesday, July 26, 75 cases of glandular fever had been reported from the Royal Free Hospital—50 nurses (including the matron), 21 medical students, 1 doctor, and 3 patients. The main hospital in Gray's Inn Road was closed to new admissions during the week-end and the branch at Liverpool Road on July 25.

Week Ending July 16

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 460, whooping-cough 1,760, diphtheria 7, measles 16,425, acute pneumonia 232, acute poliomyelitis 120, dysentery 596, paratyphoid fever 16, and typhoid fever 7.

June Quarter in England and Wales

In England and Wales in the second quarter of 1955 live births numbered 171,191, giving a rate of 15.5 per thousand population. This is the lowest rate for a June quarter in any peace-time year since 1936. In that year the rate was also 15.5, but the number of births was much lower (157,652). 124,169 deaths were registered, giving a rate of 11.2 per thousand population, compared with a rate of 10.6 in the second quarter of 1954 and 10.4 in the second quarter of 1953. Deaths of children under 1 year of age numbered 4,125, giving a new record low rate for a June quarter of 24.4 per thousand related live births, compared with a rate of 24.7 in the second quarter of 1954 (the previous record). 4,017 stillbirths were registered, giving a rate of 22.9 per thousand live and stillbirths, compared with a rate of 23.1 in the corresponding quarter of 1954.—*Registrar-General's Weekly Return*, No. 28.

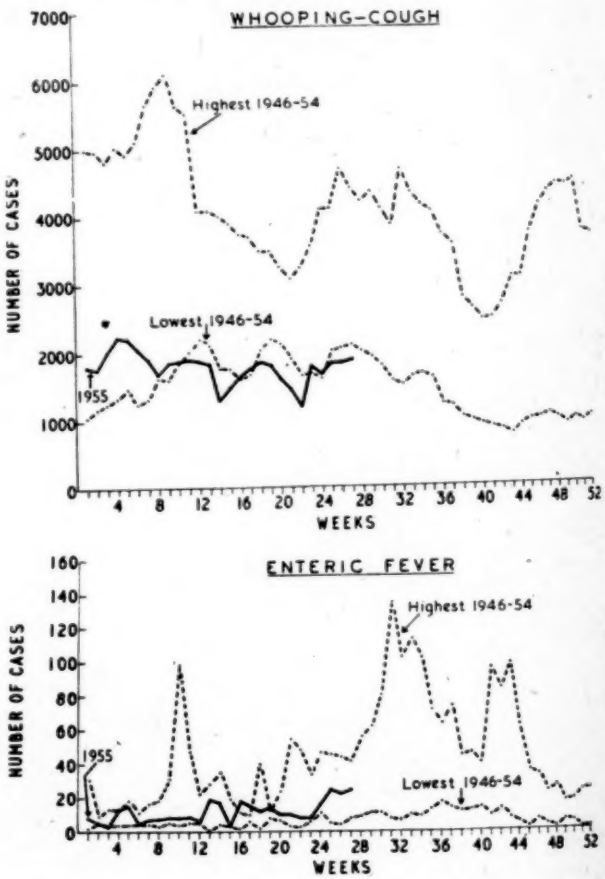
England and Wales in 1954

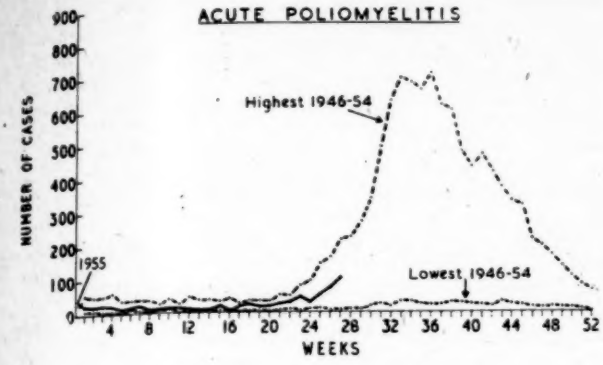
In England and Wales in 1954 the death rate was 11.3 per 1,000 of the population, being 0.1 below the rate for 1953 and the same as the rate for 1952. Figures for several causes of deaths reached record low levels. Deaths from respiratory tuberculosis numbered 7,069, compared with 7,913 in 1953 and 9,335 in 1952. Only 9 deaths were attributed to diphtheria, compared with 23 and 32 in 1953 and 1952 respectively. The number of deaths from whooping-cough fell from 243 in 1953 to 139 in 1954. Only 50 deaths from measles were recorded, compared with 245 in the preceding year and 141 in 1952, which was the previous lowest level of deaths; but the number of notifications in 1954, 147,000, was also very low, being only one-third of the number recorded in the preceding year.

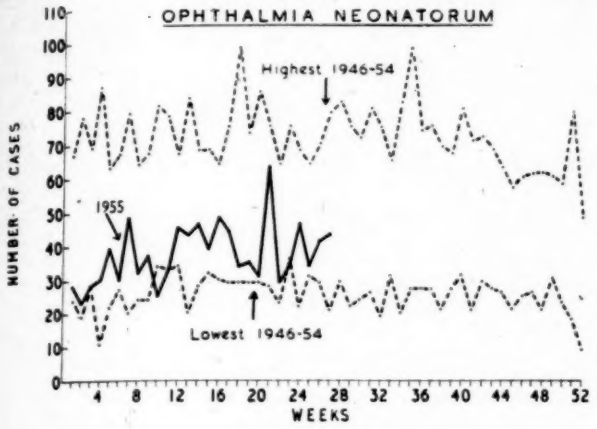
In contrast to these causes of death several main groups of causes showed an appreciable increase. The deaths from vascular lesions affecting the central nervous system numbered 72,144, being an increase of 4,075 on the total for the preceding year. Deaths from coronary-artery and arteriosclerotic disease rose from 61,751 in 1953 to 66,901 in 1954. 5,477 deaths were attributed to ulcer of the stomach and duodenum, and these were 215 more for males and 136 more for females than in the preceding year. Cancer of the lung accounted for 13,996 male deaths and 2,336 female deaths, and these totals were 1,115 more for males and 85 more for females than in 1953. 20,866 persons died from violence, an increase on the preceding year of 295 males and 707 females. 3,422 males and 1,166 females died as a result of motor-vehicle accidents, a rise of 80 for males and 133 for females compared with 1953. Accidental falls accounted for 2,118 male and 3,235 female deaths, these being 331 and 423, respectively, more than in the preceding year. The number of deaths from suicide was 3,178 males and 1,865 females, an increase of 158 and 131, respectively, on the totals for 1953.—*Registrar-General's Quarterly Return for England and Wales*, No. 425.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

The largest fluctuations in the numbers of notifications of infectious diseases in England and Wales during the week ending July 9 were increases of 659 for measles, from 17,716 to 18,375, 32 for whooping-cough, from 1,833 to 1,865, and 26 for acute poliomyelitis, from 73 to 99, and decreases of 217 for dysentery, from 807 to 590, and 29 for scarlet fever, from 585 to 556.

The largest falls in the incidence of measles were 200 in Hertfordshire, from 570 to 370, 133 in Warwickshire, from 462 to 329, 120 in Leicestershire, from 764 to 644, and 101 in Northumberland, from 317 to 216, and the largest rises were 118 in Devonshire, from 747 to 865, 108 in Yorkshire East Riding, from 192 to 300, 106 in Staffordshire, from 545 to 651, 92 in Somersetshire, from 256 to 348. The largest fall in the number of notifications of scarlet fever was 39 in Lincolnshire, from 53 to 14. The largest variations in the trends of whooping-cough were a rise of 32 in Durham, from 90 to 122, and a fall of 36 in Lincolnshire, from 96 to 60. 10 cases of diphtheria were notified, being 4 more than in the preceding week. The only counties with multiple cases were Staffordshire 3 and Lancashire 3 (Liverpool C.B. 2).

99 cases of acute poliomyelitis were notified, and these were 15 more for paralytic and 11 more for non-paralytic cases than in the preceding week. The largest returns were London 21 (Stepney 9, Hammersmith 2, Hampstead 2, Poplar 2, St. Pancras 2, Shoreditch 2), Yorkshire West Riding 15 (Barnsley C.B. 5, Dewsbury C.B. 2, Darton U.D. 2), Lancashire 10 (Liverpool C.B. 4, Barrow-in-Furness C.B. 3), Warwickshire 8 (Birmingham C.B. 6), Middlesex 5.

Notifications of dysentery were the lowest for 24 weeks. The chief centres of infection were Lancashire 215 (Liverpool C.B. 53, Blackpool C.B. 26, Manchester C.B. 25, Audenshaw U.D. 11, Swinton and Pendlebury M.B. 10), Yorkshire West Riding 59 (Leeds C.B. 18, Doncaster C.B. 10), London 41 (Islington 9), Durham 40 (South Shields C.B. 11), Surrey 21 (Croydon C.B. 16), Middlesex 21, Northumberland 19, and Yorkshire North Riding 18 (Middlesbrough C.B. 16).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 9** (No. 27) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	10	0	3	0	1	19	3	2	0	2
Dysentery	590	41	268	15		711	115	148	6	1
Encephalitis, acute	1	1		0		7	0	0	0	
Enteric fever:										
Typhoid	17	1	0	0		3	0	0	1	0
Paratyphoid	8	0	1	0		5	0	0	0	0
Food-poisoning	241	28		1		405	14		1	0
Infective enteritis or diarrhoea under 2 years				12	14				11	17
Measles*	18,375	380	107	186	243	2,690	121	74	191	223
Meningococcal infection	27	3	10	0	2	14	0	15	0	1
Ophthalmia neonatorum	43	3	3	0		21	3	8	0	
Pneumonia†	236	13	117	3		248	12	102	0	
Poliomyelitis, acute:										
Paralytic	62	9	6	1	2	46	4	12	0	0
Non-paralytic	37	12				19	2			
Puerperal fever§	223	38	8	1		237	43	5	1	0
Scarlet fever	556	41	75	31	24	807	56	111	29	35
Tuberculosis:										
Respiratory	660	86	133	17		749	99	150	25	
Non-respiratory	131	7	24	6		119	9	22	2	
Whooping-cough	1,865	81	0	84	60	2,085	98	171	23	90

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	1	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	1	0	0	7	2	0	0	2
Influenza	2	0	0	0	2	0	0	0	1	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	134	9	20	6	8	130	19	11	12	4
Poliomyelitis, acute	1	1			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	55	8	11	0	3	80	12	10	1	4
Non-respiratory		2	0	0	1		3	12	0	3
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	176	22	23	7	11	208	28	29	9	13
Deaths (excluding stillbirths)	4,561	615	532	93	160	4,543	632	305	108	142
LIVE BIRTHS	7,557	1088	884	224	460	7,628	1166	921	204	452
STILLBIRTHS	181	15	22			181	21	31		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Royal College of Obstetricians and Gynaecologists.—The Governor General of Canada, the Rt. Hon. VINCENT MASSEY, P.C., C.H., and Dr. GEORGE CORNER, director of the Carnegie Embryological Laboratory, Baltimore, have been admitted to the Honorary Fellowship. Professor A. M. CLAYE (Leeds University) and Professor C. H. G. MACAFEE (Queen's University, Belfast) have been appointed Sims-Black Professors for 1956. These are travelling professorships within the Commonwealth. In addition to the new president and vice-president whose elections are noted on p. 314, the following officers of the College were re-elected: Hon. treasurer, Mr. A. C. H. BELL; hon. librarian, Mr. A. J. MCNAIR; hon. secretary, Mr. I. M. JACKSON; hon. curator of the museum, Mr. R. A. BREWS; hon. treasurer, Australian Regional Council, Dr. J. CHESTERMAN; hon. treasurer, New Zealand Regional Council, Mr. J. M. GIESEN. Dr. G. A. SIMPSON was elected hon. treasurer, Canadian Regional Council.

Travelling Awards.—The Medical Research Council announces the following travelling awards for the academic year 1955–6:

Rockefeller Travelling Fellowships in Medicine.—Dr. R. M. ACHESON, medical registrar, Radcliffe Infirmary, Oxford; Mr. K. DALZIEL, Nuffield graduate assistant, Department of Biochemistry, Radcliffe Infirmary, Oxford; Dr. G. L. LE BOUVIER, assistant bacteriologist, Virus Reference Laboratory, Colindale, London; Dr. A. W. M. SMITH, medical registrar, Royal Infirmary, Edinburgh; Dr. W. H. J. SUMMERSKILL, registrar and tutor, Postgraduate Medical School, London; and Dr. J. VALLANCE-OWEN, senior medical registrar and medical tutor, Postgraduate Medical School, London.

Eli Lilly Travelling Fellowships in Medicine.—Dr. J. C. DAVIS, lecturer in pathology, Liverpool University; Dr. P. A. G. MONRO, demonstrator in anatomy, University of Cambridge; and Dr. E. J. Ross, assistant, Medical Unit, University College Hospital Medical School, London.

Lederle Travelling Fellowship in Medicine.—Dr. J. D. JUDAH, senior lecturer, Department of Morbid Anatomy, University College Hospital Medical School, London.

Alexander Pigott Wernher Memorial Travelling Fellowship in Otology.—Dr. R. HINCHCLIFFE, officer in charge of the Royal Air Force Acoustics Laboratory.

French Exchange Scholarships in Medical Science (in association with the Centre National de la Recherche Scientifique).—Dr. I. M. DUGUID, lecturer in anatomy, Aberdeen University; and Mr. J. D. MORELAND, postgraduate student, Technical Optics Section, Imperial College, London.

Royal Institute of Public Health and Hygiene.—The Harben Medal of the Royal Institute of Public Health and Hygiene was presented to LORD ADRIAN, P.R.S., Master of Trinity College, Cambridge, and the Smith Award (a bronze figure of Hygeia) to Dr. KENNETH COWAN, Chief Medical Officer, Department of Health for Scotland, at a special meeting of the Institute on July 20, over which Sir ARTHUR MACNALTY presided. The citations, read by Dr. J. A. STRUTHERS, stated that the Harben Medal was instituted in 1894, to be conferred every third year for eminent services rendered to public health. Among its recipients had been Pasteur, Lister, Koch, Metchnikoff, and more recently Dale, Fleming, Boyd-Orr, and Dodds. Lord Adrian was a man of outstanding distinction, President of the Royal Society, and carrying the degrees of many universities in various parts of the world. His chief sphere of work was in neurophysiology, and perhaps it might be said that his researches were in the exploration of those realms where body, mind, and spirit met. The first recipient of the Smith Award was Dr. David Niven, then medical officer of health for Glasgow, followed by Dr. Hope, of Liverpool. Among recipients happily still living were Sir William Savage, Dr. James Fenton, and Dr. Montagu Morgan, medical officer of the Port of London. Dr. Cowan had recently been appointed to a national position, but his main work hitherto had been done in the counties of Gloucestershire and Essex. He had also been chairman of the Public Health Committee of the British Medical Association. He had shown professional attainments and administrative ability of a high order. In reply, LORD ADRIAN said that his father had spent most of his life as an official of the Local Government Board, retiring at the time that department became the Ministry of Health, so that he had at any rate that family connexion with preventive medicine. All that he himself had done had been of an academic nature, and he felt it a great compliment that work of that kind should have earned this distinction. Dr. COWAN said that great advances in preventive medicine had been made in the course of the last 50 years. The people who had actually done the work had been assistant medical officers, nurses, and other staff, and last of all the medical officer of health. He looked forward to still greater advances in this field during the second half of the century.

Aldosterone Synthesized.—The synthesis of aldosterone, the adrenal hormone concerned with sodium, potassium, and water metabolism, was announced last week at the fourteenth International Congress of Pure and Applied Chemistry in Zurich. Dr. A. WETTSTEIN, in collaboration with Dr. J. SCHMIDLIN, of the research laboratories of Ciba Ltd., Basle, reported a thirty-stage synthesis of racemic aldosterone. Biological tests on the synthetic material confirmed its activity. Aldosterone was first isolated in crystalline form two years ago by British and Swiss investigators working in collaboration—Simpson and Tait, of the Middlesex Hospital, and Reichstein, von Euw, Wettstein, and Neher, in Switzerland (see *Journal*, June 5, 1954, p. 1311).

Rockefeller Institute for Medical Research, New York.—The semi-annual list of publications of the staff of the Rockefeller Institute for Medical Research, New York (No. 78: November 1, 1954–May 1, 1955) is now available. Copies of these lists will be sent regularly upon request to the Publication Service, The Rockefeller Institute, New York 21, New York.

"Prophylactic Packets."—Included in the evidence of the Association for Moral and Social Hygiene, submitted last month to the interdepartmental committee on the law relating to homosexual offences and prostitution, is a recommendation that the issue of "prophylactic packets" to National Service men should cease. "The extended use of prophylactic precautions against venereal diseases, particularly through the issue of prophylactic packets to Service men during the war, and to National Service men since the war," says the association's evidence, "has always been known to encourage men to indulge in sexual promiscuity. In some cases men have been required to produce these packets before leave to depart is given. The practical lesson of the prophylactic packet can only be offset to a limited extent by the work of chaplains, or of really good medical officers with the right moral outlook." The Association for Moral and Social Hygiene, whose president is LORD BALFOUR OF BURLEIGH, a former chairman of the Medical Research Council (1936–48), was giving evidence on this occasion on behalf of 17 other societies in addition to its own membership.

Royal Society of Medicine.—At a ceremony in London on July 14 Sir WILLIAM GILLIATT, president of the Royal Society of Medicine, conferred Honorary Fellowships on the following: Sir WILFRED FISH, chairman of the Dental Board of the United Kingdom; Professor W. R. HESS, emeritus professor of physiology, Zurich University, and joint winner in 1949 of the Nobel Prize in Medicine; Sir GEOFFREY JEFFERSON, F.R.S., emeritus professor of neurosurgery, Manchester University; Dr. I. W. MAGILL, honorary consultant anaesthetist, Westminster Hospital; Professor A. H. OLIVECRONA, professor of neurosurgery, Karolinska Institutet, Stockholm; and (*in absentia*) on Professor EMIL NOVAK, associate professor of obstetrics at Maryland University, U.S.A.

Leeds University.—At the meeting of the University council on July 20 leave of absence was given to Professor P. J. MOIR, dean of the Medical Faculty and professor of surgery, to allow him to visit Canadian and American medical schools during September and October. The title of reader in medicine was conferred on Dr. D. TAVERNER, and the title of reader in epidemiology on Dr. C. W. DIXON, both of whom held appointments as senior lecturers in the Medical Faculty. Dr. STEPHANIE M. LEESE was appointed lecturer in child psychiatry from October 1.

"Biochemical Journal."—Dr. A. NEUBERGER, F.R.S., is resigning from the chairmanship of the Editorial Board of the *Biochemical Journal* on October 1. The committee of the Biochemical Society has appointed Dr. A. G. OGSTON, F.R.S., as his successor. The editorial office of the *Biochemical Journal* will be transferred from the National Institute for Medical Research, Mill Hill, to the Lister Institute of Preventive Medicine, Chelsea Bridge Road, London, S.W.1, as from September 1. From that date communications to the secretary to the Editorial Board should be sent to the new address.

Supplies of Laboratory Animals.—Guinea-pigs, frogs, and toads are now very scarce, according to the July *News Letter* of the Laboratory Animals Bureau, while ferrets, plentiful at present, are likely soon to become so. This is owing to the devastation of the rabbit population in Britain by myxomatosis; ferreting has virtually ceased and consequently the commercial breeding of ferrets is at a standstill. Up-to-date information on animal supplies can always be obtained from the Laboratory Animals Bureau, M.R.C. Laboratories, Holly Hill, Hampstead, London, N.W.3.

"Journal of Tropical Pediatrics."—The first issue of this quarterly journal on problems of child health in subtropical and tropical countries appeared in June, price 5s., the annual subscription being 21s. (post free). It is edited by Dr. D. B. JELLIFFE, of the All-India Institute of Hygiene and Public Health, Calcutta, assisted by an internationally composed editorial advisory board. The journal's primary aims are to provide a forum for the discussion of problems of "preventive child care" in subtropical and tropical regions, and to publish original work on all aspects of tropical paediatrics. The editorial offices are at Harrington Court, Harrington Street, Calcutta. Subscriptions may be placed with the publishers, *Journal of Tropical Pediatrics*, Effingham House, Arundel Street, London, W.C.2.

Empire Rheumatism Council.—The Hon. J. J. ASTOR, chairman of the Middlesex Hospital and of the Times Publishing Company, has been elected a vice-president of the Empire Rheumatism Council.

Professor J. H. Dible has had conferred on him the title of Professor Emeritus of Pathology in the University of London on his retirement from the Chair of Pathology at the Postgraduate Medical School of London.

"Family Doctor."—The August number contains articles on slipped disks (by Mr. JOHN CHARNLEY), duodenal ulcer (by Dr. ROBERT KEMP), and retroversion (by Dr. G. P. MILNE) as the principal medical contributions. The 6-page lay version of "Any Questions?", called "Family Doctor Answers," deals with such subjects as glaucoma, beryllium poisoning, infantile eczema and vaccination, glandular fever, and inhalers for nasal congestion. *Family Doctor* costs 1s. 6d.

COMING EVENTS

British Hospitals Contributory Schemes Association (1948).—The annual conference will be held on September 29 and 30 at Caxton Hall, Westminster. The principal speakers will be: The MINISTER OF HEALTH, Mr. IAIN MACLEOD, and Mr. L. HART, whose subject is "The New Australian Health Service." Details from the association, Royal London House, Queen Charlotte Street, Bristol, 1.

European Association Against Poliomyelitis.—The third symposium will be held at Zurich on September 29 and 30. The subjects for discussion will be poliomyelitis vaccination, treatment in the acute stage, prevention of deformities, aggravating factors, and controlled respiration. Further details from Dr. P. RECHT, 67, Boulevard Auguste Reyers, Brussels.

NEW ISSUES

British Heart Journal.—The new issue (Vol. 17, No. 3) is now available. The contents include:

EISENMENGER'S COMPLEX. James W. Brown, Donald Heath, and William Whitaker.
DISSOCIATION WITH INTERFERENCE, RECIPROCAL RHYTHM, AND CORONARY SINUS RHYTHM. Evan Fletcher and Maude Stevenson.
THE SERUM CHOLESTEROL AND OTHER LIPIDS AFTER ADMINISTRATION OF SITOSTEROL. J. M. Barber and A. P. Grant.
SERUM LIPOPROTEIN PATTERNS IN CORONARY SCLEROSIS AND ASSOCIATED CONDITIONS. M. F. Oliver and G. S. Boyd.
THE EFFECT OF EXERCISE ON LUNG DISTENSIBILITY AND RESPIRATORY WORK IN MITRAL STENOSIS. Graham W. Hayward and J. M. S. Knott.
PULMONARY HYPERTENSION ASSOCIATED WITH NECROTIZING PULMONARY ARTERITIS. J. D. Aitchison and H. G. Richmond.
AGE AND SEX FACTORS IN CORONARY ARTERY DISEASE. A. A. Fitzgerald Peel.
THE HEART SOUNDS AND THE ARTERIAL PULSE IN CONGENITAL AORTIC STENOSIS. John Rienhold, Ulf Rudhe, and R. E. Bonham-Carter.
THE PATHOLOGY OF ENDOMYOCARDIAL FIBROSIS IN UGANDA. J. N. P. Davies and J. D. Ball.
PHONOCARDIOGRAPHY IN ACUTE RHEUMATIC CARDITIS. E. M. M. Besterman.
CONGENITAL AORTIC STENOSIS AND ITS SURGICAL TREATMENT. R. M. Marquis and Andrew Logan.
THE RAUWOLFIA ALKALOIDS IN THE TREATMENT OF HYPERTENSION. Maurice McGregor and N. Segal.
CARDIAC PAIN IN ASSOCIATION WITH MITRAL STENOSIS AND CONGENITAL HEART DISEASE. Douglas Stuckey.
SIR ARTHUR KEITH.
CASE REPORTS:
TRAUMATIC AORTO-PULMONARY FISTULA. A. D. Gillanders.
COR TRILOCULARE BIATRIATUM: FINDINGS AT THORACOTOMY. C. E. Drew, P. R. Fleming, and A. M. Johnson.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

APPOINTMENTS

BARCLAY, DAVID, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health, City of Aberdeen.

BOURNE, HAROLD, M.B., B.S., D.P.M., Lecturer in Psychiatry and Junior Physician, University of Otago Medical School, Dunedin, New Zealand.

DUFFY, JOHN, M.D., F.R.C.P.I., D.P.H., T.D.D., Medical Superintendent, James Connolly Memorial Chest Hospital, Blanchardstown, Co. Dublin.

GILLET, JOSEPH ADRIAN, M.B., Ch.B., D.P.H., Medical Officer of Health to Dagenham Borough and Area Medical Officer to Essex County Council.

MEARA, R. H., M.B., B.Chir., M.R.C.P., Assistant Consultant Physician for Diseases of the Skin, Middlesex Hospital, London, W.

RITCHIE, E. A. A., M.B., M.R.C.P., D.P.M., Senior Assistant Psychiatrist, Rauceby Hospital, Sleaford, Lincolnshire.

WARREN, STANLEY ROBERTSON, M.B., Ch.B., D.P.H., Medical Officer of Health, Brentwood Urban District Council, Assistant County Medical Officer of Health, Essex County Council.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bell.—On July 17, 1955, at Edinburgh, to June (formerly Cross), wife of David James Bell, F.R.S.Ed., a second daughter.

Kenyon.—On July 10, 1955, at the Radcliffe Infirmary, Oxford, to Dr. Nuala (formerly Gilmore), and Dr. W. Islay Kenyon, Maids Moreton, Buckingham, a son—Angus Peter Richard.

Measday.—On July 15, 1955, at Harpenden Memorial Hospital, Herts, to Jean (formerly Randall), M.B., B.S., wife of Brian Measday, M.B., B.S., 7, Deauville Mansions, London, S.W., a son.

DEATHS

Bennett.—On June 25, 1955, at Guildford County Hospital, Richard Shaw de Courcy Bennett, M.R.C.S., L.R.C.P., Major, R.A.M.C., retired, aged 70.

Blair.—On June 12, 1955, at Bath, Somerset, Alexander Blair, M.B., B.Ch., D.T.M.&H., of Upper Westwood, Bradford-on-Avon, Wilts.

Brereton.—On May 23, 1955, at "Woodlands," Tonyrefail, Glam., John Edward Brereton, L.R.C.P.&S.I. & L.M.

Daly.—On June 21, 1955, at Royal Victoria Hospital, Netley, Hants, Frederick James Purcell Daly, M.R.C.S., L.R.C.P., aged 77.

Graham.—On June 16, 1955, at Wyndham Lodge, Milford, Surrey, George Frederick Graham, M.D., F.R.C.S.I., Lieutenant-Colonel, I.M.S., retired.

Green.—On June 25, 1955, at 26A, Winn Road, Southampton, Hants, Arthur Robert Green, M.R.C.S., L.R.C.P., F.S.A., aged 89.

Hodgson.—On June 17, 1955, at his home, Henley-on-Thames, Oxon, Ernest Charles Hodgson, D.S.O., M.R.C.S., L.R.C.P., Colonel, I.M.S., retired, aged 76.

Lucas.—On June 12, 1955, at his home, Weatherhill Farm, Icklingham, Suffolk, Travis Clay Lucas, M.B., B.Ch., D.P.H., Major, R.A.M.C., retired, aged 78.

Lupton.—On June 5, 1955, at St. Mary Abbots Hospital, London, S.W., Alfred Crichton Lupton, M.B., C.M., Surgeon Captain, A.M.S., retired, of the Onslow Court Hotel, London, S.W., aged 83.

Sutherland.—On June 14, 1955, at 21, Belmont Avenue, Baildon, Yorks, William Sutherland, M.D.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Malaria Prophylaxis at Ports of Call

Q.—*Should malaria prophylactics be given to ship's passengers and crew before going ashore at ports where malaria is prevalent, or is this unnecessary? They would return to the ship for the night. If so, what regime should be adopted?*

A.—Mosquitoes of the species transmitting malaria with but rare exceptions do not bite during daylight. There is therefore virtually no risk of passengers contracting malaria if they return to the ship before nightfall. To those who stay ashore after this time, again the risk is minimal if they wear clothing which covers all the body except the hands and face, or if to exposed areas of skin a mosquito repellent such as dimethyl-phthalate is applied. In ports such as the majority of those of India and the Far East, in which the prevalent form of malaria is that due to infection with *Plasmodium vivax*, these precautions only are sufficient. Where the more dangerous *P. falciparum* infection is common, however, as in tropical Africa, it is advisable also to recommend that 100 mg. proguanil should be taken daily while going ashore and for 14 days thereafter. An alternative prophylactic is chloroquine in doses of 0.3 g. (base) weekly while the ship is in port and for two weeks afterwards.

International Vaccination Certificates

Q.—*What procedure should be followed in issuing international smallpox vaccination certificates?*

A.—New forms of international certificates against smallpox, yellow fever, and cholera came into force on October 1, 1952, and a note on the new certificates, prepared by the Ministry of Health, was published at the time in the *Journal*.[1]

In the case of primary vaccination against smallpox the site of the vaccination must be inspected after a suitable interval, and the result must be recorded on the form. To quote from the regulations: "If a first attempt at primary vaccination fails, subsequent attempts should not be regarded as revaccination: at least two more attempts with different vaccine are recommended, each attempt (with its date) being recorded on the certificate and each failure being shown as unsuccessful. If such a certificate is produced abroad the question of further vaccination will then be one for the health authorities there to whom such a certificate may be produced."

"'Duplicate' international certificates should not be issued. When a person has lost an international certificate the doctor who performed the vaccination may be prepared, if he has the necessary records, to issue a new certificate. Any such new certificate should be dated as in the original, and it should not be marked 'duplicate' or 'copy.' If that doctor is not available, or if the record of the original vaccination cannot be traced, it is recommended that the person should be revaccinated and be given a new certificate."

Recording of the result of vaccination is *not* required for revaccination.

The smallpox vaccination certificate becomes valid eight days after the date of a *successful* primary vaccination, and remains valid for three years. In the event of revaccination, the certificate becomes valid on the date the vaccination is performed, irrespective of when the previous period of validity expired.

The appropriate international vaccination certificate form must be duly dated and signed by the vaccinator, who is advised to add the initials of his medical qualifications. An approved stamp is placed on every form to authenticate the identity of the vaccinator as a doctor, the authenticating authority being the health officer of the town, urban district, or rural district council of the area in which the doctor practises. Forms of certificate can be obtained from the Government health department concerned, or from travel agencies, airlines, or shipping companies.

REFERENCE

[1] *British Medical Journal*, 1952, 2, 774.

Action and Uses of Hyaluronidase

Q.—*What are the clinical uses of hyaluronidase and how does it act?*

A.—Hyaluronidase is an enzyme which acts on hyaluronic acid, a mucopolysaccharide which has been isolated from connective tissue. Mucopolysaccharides are probably the cement substances which bind collagen fibres together, and, when they are broken down by hyaluronidase, substances introduced into the tissue spaces tend to spread more widely than they otherwise would. Thus it is possible to introduce relatively large amounts of fluids such as normal saline or isotonic dextrose solution into the subcutaneous tissues of infants or of adults with no suitable veins for cannulation. It is possible to obtain good pyelograms in infants by the use of diodone mixed with hyaluronidase and injected subcutaneously. Hyaluronidase may be used to help to disperse traumatic exudates such as haematomata or irritant solutions accidentally extravasated round a vein. Hyaluronidase added to local analgesic solutions increases the area of analgesia and is said to enable fractures to be manipulated painlessly. It is a relatively non-toxic substance, and, although it is a protein, it does not easily give rise to sensitization.

Subacute Combined Degeneration of the Cord

Q.—*How quickly after defaulting from regular vitamin B_{12} therapy might a patient with subacute combined degeneration of the cord be expected to show (a) haematological and (b) neurological signs of regression? What factors influence the speed of regression?*

A.—It is not possible to forecast accurately how long it will take for a patient to show evidence of haematological or neurological relapse after discontinuance of regular treatment with cyanocobalamin (vitamin B_{12}), because every patient differs in response to therapy. In general, however, a patient who previously was anaemic before treatment began may show a gradual fall in the blood count in the course of a few months (varying from 1 to 12), but very occasionally much longer intervals may be noted. Where there had been originally little or no anaemia discontinuance of treatment may not be followed by haematological relapse for a long time, if at all.

The same may be said of the neurological signs and symptoms. Some patients may go for several months before showing partial regression after discontinuance of treatment, although in my experience the earlier signs of peripheral neuritis, pins and needles, numbness and cramps, and vague neuritic pains may often appear quite early, even as soon as a week after cessation of treatment. The onset of both neurological and haematological relapses can be quite sudden or only very gradual.

As regards the factors influencing the speed of relapse, the amount of the anti-anaemic factor that is stored in the body depots is important. The patient who has had intensive treatment at weekly or fortnightly intervals will be much slower in relapsing than the one who has been receiving minimal doses over longer intervals of, say, three to four weeks, or who has been given so-called depot therapy at monthly or two-monthly intervals. Other factors that must be borne in mind are whether the patient is on a normal diet or is taking a diet with inadequate protein and vitamins. The most potent factors in accelerating the rapid onset of both haematological and neurological relapses are severe infections—such as influenza, pneumonia, cystitis—pregnancy, malignant disease, and similar added burdens on the

haematopoietic system. These patients have a greater tendency than the average to develop diabetes, thyroid disturbances, and neoplastic changes, all of which will tend to accelerate a return of the signs and symptoms of pernicious anaemia or subacute combined degeneration of the cord.

Finally, another therapeutic agent, folic acid, which is a frequent constituent of many proprietary anti-anaemic preparations, is a very potent and rapid producer of subacute combined degeneration of the cord, and must never be given to patients with pernicious anaemia, whether there are neurological complications or not.

Effect of Contraception on Later Fertility

Q.—*I have been asked by a young married couple, both partners being aged about 25, whether the practice of contraception over the next three years would impair their fertility. I wonder if you could help me to answer this.*

A.—Provided that the method adopted is an approved one (for example, Dutch cap or condom used in conjunction with a reputable spermicidal jelly), there is no evidence to show that contraception lowers subsequent fertility. Deferment of pregnancy does, however, allow the age factor to operate, so that at least the woman is likely to be slightly less fertile at the age of 28 years than she is now.

Ultraviolet Light for Indolent Ulcers

Q.—*Does ultraviolet light promote the healing of indolent ulcers such as bedsores and varicose ulcers?*

A.—Ultraviolet light, which has but feeble power of penetration of intact skin, may nevertheless be expected to have a stimulant effect when applied direct to a raw surface such as an ulcer, and this seems to be borne out in practice. It should be employed, however, only when no remediable cause for the ulcer can be discovered, and this scarcely applies to varicose ulcers and bedsores; here the correct treatment is to deal with the primary cause, although ultraviolet may sometimes be used as an adjuvant to bring about more rapid response. In both cases care must be taken to protect the surrounding skin, by metallic screening, from the effects of the rays.

Tetany in a Hot Climate

Q.—*We have seen several cases of tetany in this area (Thailand). A moderate case with carpo-pedal spasm in a puerperal woman responded very rapidly to intravenous calcium gluconate. More severe cases with generalized convulsions and rigid abdomens have improved only slightly in the first half-hour, but by the next day have recovered except for muscle stiffness or pains. Does this suggest that the latter are not true hypocalcaemic cases? The textbooks at hand give as one cause "hyperventilation in hot humid climates" (conditions apply), but do not make clear whether there is hypocalcaemia or whether intravenous calcium is of any benefit in such cases. If it is not, what treatment is recommended? How is one to differentiate clinically between the two types?*

A.—Muscular irritability can be increased by a rise in plasma *p*H in the absence of any lowering of the plasma calcium; and this type of tetany would not respond to calcium gluconate in the same rapid way as hypocalcaemic tetany. Such a rise in *p*H could well be induced by hyperventilation, which in temperate climates is usually a "voluntary" phenomenon associated with psychoneurotic illness; in hot humid conditions it may happen spontaneously. Tetany, and other symptoms, due to hyperventilation can be terminated by rebreathing into a paper-bag; they can also be induced by voluntary overbreathing. The plasma calcium should be normal, the plasma bicarbonate low, and the plasma *p*H raised; in an acute attack the urine should be alkaline and effervesce on the addition of acid. It is possible that even under tropical conditions an episodic hyperventilation tetany could owe something to personality disorder, and might benefit from reassurance and a demonstration of the reversibility of the symptoms by rebreathing. Disturbances of magnesium and potassium metabolism may also lead to tetany, but there seems no good reason to suspect such causes in the instance given. Another somewhat different possibility to be considered is water-intoxication, which can cause both muscle cramps and generalized convulsions; this could arise if much water was drunk by patients who had sweated freely. Convulsions from this cause would respond to intravenous injection of 20 ml. of 10% saline.

"Pituitrin Shock"

Q.—*Is there such a condition as "pituitrin shock"? I remember, when dealing with incomplete abortions, that the giving of "pituitrin" sometimes produced a condition resembling shock, but I cannot find reference to this in the textbooks. Is this a recognized syndrome? If so, what is the aetiology?*

A.—The condition of "pituitrin shock" has been recognized for at least 25 years and possibly longer, and was the subject of a paper by M. H. Adelman and B. B. Lennon in 1941.[1] It is mentioned in most of the larger obstetric textbooks, but is not perhaps stressed so much recently because in obstetric practice pituitrin has been superseded by ergometrine and by relatively pure preparations of oxytocin. One of the main reasons for pituitrin's loss of popularity is its tendency to produce severe and even fatal shock. Pitruitin is a trade name for a relatively crude extract of the posterior lobe of the pituitary, and it contains both vasopressor and oxytocic factors. It can produce an anaphylactic reaction with skin manifestations as well as collapse, especially in a patient sensitized by previous injections. The typical "pituitrin shock," however, is believed to be caused by vasopressin, the probable mechanism being the production of coronary spasm. This concept is supported by the fact that modern preparations of oxytocin, which are relatively although not absolutely free from vasopressin, rarely cause circulatory disturbances even when given intravenously.

Reactions to pituitrin occur even under general anaesthesia—indeed, the combination of cyclopropane and pituitrin is especially dangerous and several fatalities are recorded as resulting from it. This particular aspect has been discussed by S. Belinkoff[2] and by several subsequent writers.

REFERENCES
[1] *Amer. J. Obstet. Gynec.*, 1941, **41**, 652.
[2] Ibid., 1944, **48**, 109.

Dangers of Treating Keloids on the Chest

Q.—*Five years ago a girl, then aged 16, developed a keloid on her chest. There was no history of injury, and the diagnosis was a clinical one. She is of Indian extraction, living in South America, and there is a history of keloid formation in a thyroidectomy scar in a sister. Two years ago the keloid was removed surgically and the site treated with deep x rays (dosage unknown), but it recurred a year ago and seems to be spreading. (1) Ought further steps to be taken to confirm the diagnosis, in view of the absence of injury in the history, and (2) what treatment is advised?*

A.—The problem posed by your correspondent is a difficult one. Firstly, it is very unlikely that a keloid would develop spontaneously. Almost always there is some antecedent injury or lesion; in this case it could well have been a mosquito bite. Secondly, the patient, being of Indian extraction, doubtless has a tendency to keloid formation, as have most people with pigmented skins. Thirdly, the keloid occurs on the chest. This is probably the commonest site for the development of such a lesion, and once it has occurred the treatment of surgery plus radiation simply makes it worse.

I should be against any form of treatment whatsoever, and would leave time to aid in the resolution of the keloid. Only too often patients, particularly girls, present themselves with moles or warts on the chest, particularly in the sternal area, and ask for their removal. Any surgeon who is foolish enough to excise such lesions will almost invariably be rewarded with a keloid several times the size of the original

lesion. The common story is then for *x*-rays to be applied with burning of the keloid, further surgery to excise the *x*-ray burn, and eventual disfigurement of the chest out of all proportion to the original lesion.

"Fluorescent Perspex"

Q.—*Is there any danger of the dust from "fluorescent perspex" causing dermatitis or ocular irritation? A display artist has been working with this material, which he cuts with a circular saw. He protects his eyes and nose with a mask, but complains of periodical itching and redness of the skin of the face, and once his eyelids swelled severely.*

A.—"Perspex" is one of the trade names for transparent sheets made from methyl methacrylate resin. In its manufacture methyl methacrylate monomer is polymerized by the action of heat in the presence of benzoyl peroxide. In many of these plastics it is the monomer which may give rise to dermatitis and irritation of the skin, whereas the fully polymerized plastics are usually inert and non-irritating. If the plastic has not been fully polymerized residues of the monomer may be left in it and the dust from it may be irritating. According to L. Schwartz, L. Tulipan, and S. M. Peck (*Occupational Diseases of the Skin*, 2nd ed., 1947, p. 476), "Dermatitis has occurred among dental technicians moulding it to make dentures. The actual irritant is said to be the monomer, a water-white liquid, used to plasticize the resin mass. The catalyst, benzoyl peroxide, may also cause dermatitis." With "fluorescent perspex" there is a further hazard from an additive, present in 2% concentration in the dust, which is known to cause dermatitis when used by itself.

Potatoes and Black Tongue

Q.—*One of my female patients who had a "black tongue" discovered that the condition completely disappeared when she stopped eating potatoes, only to reappear when she started to eat them again. Is there any explanation of this?*

A.—P. Rayer, who was first to describe "black tongue" in the second edition of his *Treatise on Diseases of the Skin* in 1835, mentions that the condition may follow the consumption of foods and medicine, and it is frequently seen after taking medicines containing iron—for example, Easton's syrup. I have not met with black tongue associated with the eating of potatoes, but it could possibly follow a change in the buccal flora after eating potatoes or an allergy to potatoes expressing itself as a localized superficial glossitis.

Spontaneous Orgasm as Cause for Abortion

Q.—*Are spontaneous nocturnal orgasms commonly experienced by pregnant women? A married woman of 34, all of whose three pregnancies have ended in miscarriages (at the second, fifth, and fourth months respectively), tells me that when pregnant she is woken by a spontaneous orgasm about once a week. Ordinarily during coitus she seldom has an orgasm. Are these spontaneous orgasms likely to have any bearing on the repeated miscarriages? The patient has been investigated for all the usual causes of habitual miscarriage, with negative results.*

A.—Although they can occur without, nocturnal orgasms usually accompany sex dreams. A high proportion of women—probably at least one-third—experience them at some time during life, both in and out of pregnancy. Their occurrence is related to overt sex experience. Thus, nocturnal orgasm is rare in women who have never been roused sexually; it is sometimes seen in women who live an active sex life, and may be precipitated by love-making before sleep; it is perhaps most common in women who after a phase of sex life are deprived of it—for example, widows. Moreover, nocturnal orgasm is not uncommon in those who fail to achieve orgasm during coitus, a possible explanation being the removal of an inhibition which is present during consciousness.

In the case in question, nocturnal orgasm is probably "compensatory" in that it is likely that the couple are abstaining from coitus with the idea of reducing the chances of another miscarriage. In other words, the orgasms are more likely to be the indirect result than the cause of the abortion habit. They do not in themselves account for the recurrence of abortion, yet it is difficult to deny that they might act as a precipitating factor in a woman already showing a tendency to abort. Their influence in this respect is not likely to be strong, but if it is wished to reduce their incidence one suggestion is to insist that husband and wife sleep in separate beds if not in separate rooms. Even light physical contact appears to precipitate nocturnal orgasms in some women.

Actual Size of Cavities on Radiographs

Q.—*What is the most accurate method of determining the actual size of a tuberculous cavity on a radiograph? What differences, if any, are there in the use of 14 × 17 in. (35.5 × 43.2 cm.) as against 4 × 5 in. (10.2 × 12.7 cm.) films for this purpose? Is it true that, the smaller the film, the more the size of a cavity will be exaggerated?*

A.—The most accurate method of determining the actual size of a tuberculous cavity is by tomography in the antero-posterior and lateral planes. It must be remembered, however, that tension cavities can vary considerably in size from time to time, depending on the degree of obstruction in the bronchus draining the cavity.

The differences in the size of a cavity on a 14 × 17 in. (35.5 × 43.2 cm.) and a 4 × 5 in. (10.2 × 12.7 cm.) film are determined not by the size of the film but by the distance at which it is taken. The cavity will look relatively bigger on the smaller film because it is taken at a shorter distance.

Dilatation of the Pupils after Alcohol

Q.—*How constant is the finding that, in the early stages of alcoholic intoxication, the pupils are dilated, as stated in the B.M.A. pamphlet, "The Recognition of Intoxication"? I have not found this always to be the case.*

A.—Laboratory observations show that blood alcohol concentrations of about 130 mg. per 100 ml. dilate the pupil by about 10%.[1] It is doubtful if this degree of dilatation would be detected by clinical methods. The clinical findings are probably largely due to excitement, which leads to over-activity of the sympathetic nervous system and excess secretion of adrenaline. This is an inconstant feature of intoxication, and absence of pupillary dilatation could certainly not be taken as evidence that a person was fit to drive a motor vehicle.

REFERENCE

[1] Skoglund, C. R., *Acta physiol. scand.*, 1943, **6**, 94.

Corrections.—The last speaker at the scientific meeting of the Faculty of Anaesthetists on July 9 (*Journal*, July 23, p. 261) was Dr. P. O. Yates, not Mr. W. Blackwood.

It is regretted that the appointment of Colonel R. G. W. Ollerenshaw as an Officer (Brother) of the Order of St. John was omitted from the list published last week (*Journal*, July 23, p. 262).

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